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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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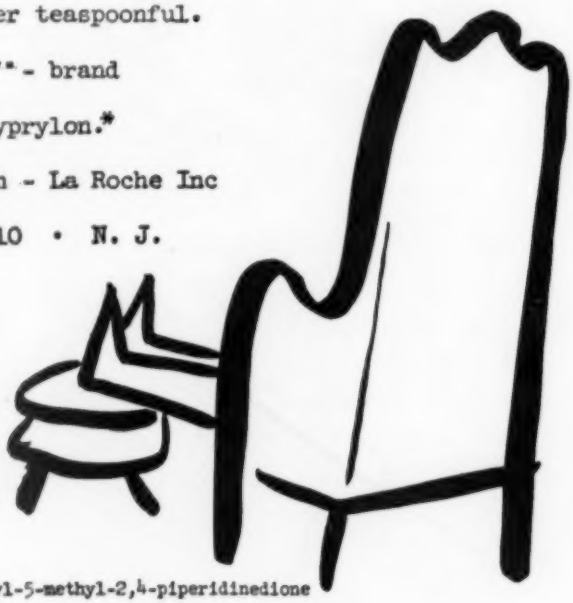

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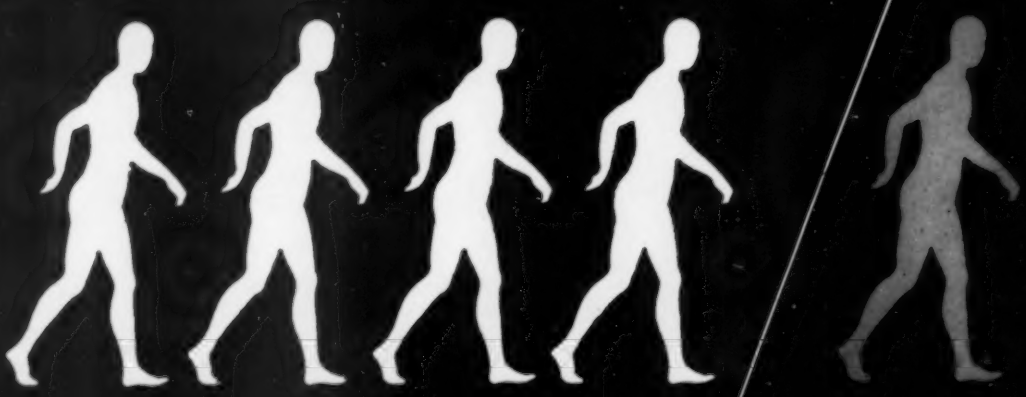

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2. Plotz, M.: N. Y. State J. Med. 52:2012 (Aug. 15) 1952.
3. Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.
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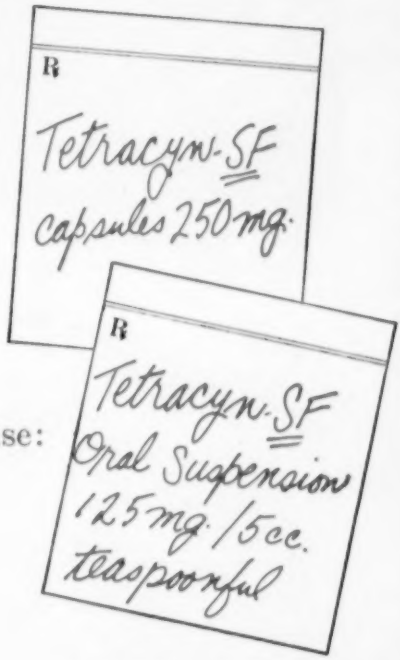

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1. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared in Collaboration with the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Washington, D. C., 1952.

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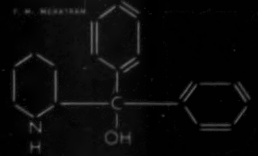

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ROBERT L. CRAIG, *Editor*

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CORTISONE, ACTH AND INFECTION*

LEWIS THOMAS

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In considering the effects of cortisone and ACTH on the process of infection, there are four general items before us, which may be defined by brief preliminary statements. First, cortisone and ACTH do cause enhancement of infection by a great variety of different infectious agents, and they appear to do so by lowering the host's resistance rather than by affecting the agents themselves. It lies before us to consider what mechanisms are involved in this effect on the host. Most of our information in this area is derived from animal experimentation, and we will become involved, inevitably but briefly, in a not altogether satisfactory area of theory and speculation. Second, cortisone and ACTH have become, within a short span of time, perhaps the most universally popular and widely accepted therapeutic agents since the introduction of purgatives, and there seems to be no human disease in which they have not, at one time or another, been given a try. It was to be expected that they would be used in infectious diseases, and it is not remarkable that they are still being used. Our problem here is to determine whether there are

* Presented at the 27th Graduate Fortnight of The New York Academy of Medicine, October 26, 1954.

particular circumstances or particular varieties of infectious disease in which the use of the hormones is justified. Third, a similar problem, but from a different point of view: under what circumstances does the use of ACTH or cortisone constitute a positive danger to the patient? And finally, we shall have to weigh certain matters. In the light of all that has been learned to date about the effects of the hormones in experimental animals and man, and in view of all that remains to be learned, what criteria should determine whether or not the hormones are to be administered? Now, this should be the last point for our discussion, and should properly come as a conclusion after all the evidence has been reviewed. However, much of what I shall say about the evidence will be colored by certain acquired prejudices, and perhaps it would be best to state, in advance, my own conclusions concerning the justifications for employing these therapeutic agents.

I would suggest that the clinical use of ACTH and cortisone should be reserved for occasions of peril, and here I would recognize only two kinds of peril: the pain of death, and the pain of prolonged or permanent incapac..ation. They should not be used for the purpose of providing comfort in what would otherwise be uncomfortable but self-limited illnesses. If, in a given situation, it becomes agreed that their only effect is temporary symptomatic relief, they should then be set aside. They should not be regarded as an improved form of aspirin. The reasons for this general prejudice are only partly based on their known effects on the process of infection – actually, complications arising from these effects in human beings have not occurred frequently enough to cause any general alarm. Nor is it because of the familiar endocrinologic side-effects – on the body shape, or the skin or the hair – although such profound degrees of metabolic dishevelment, especially when produced in young children, should give one pause. The real basis for my prejudice is that we have not yet had enough time with these hormones to be able to predict their long-range effects, and until this has been accomplished their casual routine use is difficult to justify. These are still new, poorly understood, and extraordinarily potent pharmacologic agents. Many of the things which we know about their immediate effects suggest that we should be wary and cautious for the future.

Consider several:

It has been shown that several representative species of virus are among the infectious agents whose capacity to infect is greatly enhanced

by cortisone;[1] there is reason to believe that the human organism is host to a great variety of viruses whose identities have not yet been determined and whose long-range injurious effects have not been gauged. It has been shown that malignant human neoplasms, which cannot be transplanted into normal animals, become able to grow without restraint in cortisone-treated animals.[2] Neoplasms which are ordinarily not transmissible in certain species become easily transmissible with the aid of cortisone,[3] and the induction of widespread metastasis with tumors which normally remain localized has been observed.[4] It has even been reported that the growth of tumors induced by carcinogens is augmented by cortisone.[5] It has been shown, furthermore, as we shall see shortly, that certain bacterial toxins produce, in cortisone-treated animals, necrotizing lesions of the blood vessels and kidneys which do not occur in normal animals.[6] Experimental streptococcal infections which have remained dormant and hidden for long periods of time have been reactivated to produce lethal septicemia,[7] and similar results have been observed with other types of infection.[1] Mental disturbances, which closely simulate the most malignant forms of mental disease, have occurred as a complication of therapy, and these are especially alarming when they happen, as they have, in young children.

It is difficult to be sanguine about drugs with such side-effects as these, and it is not enough to say that some of the reactions are transitory or reversible, or that they do not occur very often. If these can be the immediate effects, we should await the much later effects of treatment, especially prolonged treatment, with meticulous attention, and I submit, with some anxiety. And in the meanwhile, until the data of a decade or longer have been reviewed with care, the clinical use of these hormones should not be extended beyond the areas in which it can be predicted that they may save or prolong life, or relieve intractable suffering. This is especially to be emphasized, I believe, for the infectious diseases, in which something of a vogue for the use of cortisone and ACTH as "adjuncts" of therapy is discernible on the horizon.

Mechanisms Involved in the Effects of Cortisone on Infection

And now, having placed much of the conclusion of this paper within the introduction, we come to the first problem at hand, which is the mechanism by which cortisone and ACTH cause enhancement of infection.

The evidence for the enhancing effect has by this time become overwhelming.[1, 8] The list of hosts in which the phenomenon has been observed includes mice, rats, guinea pigs, hamsters, rabbits, dogs, monkeys, human beings, and even chick embryos. The microorganisms concerned include almost all of those which have been tried—the effect has been shown, for example, with streptococci, pneumococci, staphylococci, brucellae, typhoid bacilli, spirochetes, corynebacteriae, malaria parasites, trypanosomes, several varieties of fungi, and the viruses of poliomyelitis, influenza, Coxsackie disease and rabbit fibromatosis. It would appear that this is the kind of almost universal biological phenomenon which should lend itself easily to investigation, and one might expect much to have been learned about the mechanisms concerned. It is sad to report that this is not the case. Despite the most intensive study by a great many workers, no satisfactory explanation of the effect is yet available. Several hypothetical possibilities have been offered, all of them equally plausible, but all of them still unproved.

The response of rabbits to infection by Group A hemolytic streptococci[9] will serve as a good example of the effect of cortisone. Normal rabbits are extremely resistant to infection by streptococci, and heavy concentrations of live organisms can be injected into the skin with no result other than a vigorous, well-localized inflammatory reaction. Within about twenty-four hours, there is edema, erythema, induration and sometimes central necrosis, at the injected skin site. Bacteremia does not occur, and the rabbits show no evidence of systemic illness.

When the animals are treated with cortisone for three days prior to infection, in doses of 5 mg. per kilo, an altogether different response occurs. There is no evidence of local inflammation—indeed, twenty-four hours after the injection of streptococci there is often no way of telling where the injection was made, or at best a flat zone of erythema with no edema or induration, but at this time, and on each day thereafter for as long as the animal survives, blood cultures show literally tens of thousands of streptococci per cc. of blood. Surprisingly enough, the animals do not seem at first to be troubled by this extraordinary septicemia—they eat, drink and move about much in the manner of normal rabbits. After three or four days they begin to die, usually suddenly, convulsively, and without warning. At autopsy, the organs show no significant gross changes, but on histologic examination they are found to be swarming with streptococci. Massive colony-like ac-

cumulations of bacteria are most frequently observed in the heart, where they grow in masses between muscle fibers. Despite their presence, there is little or no evidence of tissue reaction and no local inflammatory cell response. One gains the general impression that the entire animal has been converted into an inert culture medium for streptococci.

This, then, is an example of what cortisone can do when it is given prior to streptococcal injection. Another effect, perhaps more important, is the action on latent infection, which can be demonstrated by giving cortisone long after a streptococcal infection has apparently subsided.

Several years ago Denny and the author[7] showed that Group A streptococci are capable of persisting in the tissues of infected rabbits for long periods of time, without giving rise to bacteremia, abscess formation or other signs of localized infection. As late as eight weeks after an intravenous injection of living streptococci, in normal rabbits, it is possible to recover the organism from 25 per cent of animals by making cultures of whole pieces of heart, liver or kidney tissue, even though blood cultures have been negative and the animals have appeared to be enjoying good health throughout this period.

In animals with this type of chronic, latent streptococcal infection, cortisone treatment results in streptococcal bacteremia. To illustrate, a group of four rabbits were infected by an intravenous injection of a type 24 strain of streptococcus. Two months later a series of daily blood cultures were made, all of which were negative. Cortisone was then begun, in a dose of 25 mg. each day. Within four days, streptococcal bacteremia was present in two of the animals. Cortisone was stopped, and the blood cultures promptly became negative. At the end of three and a half months cortisone was again administered, and again one of the animals developed streptococcal bacteremia.

The effect of cortisone on the local skin reaction to streptococci deserves some attention, since it provides a circumstance in which both the harmful and apparently beneficial actions of cortisone can be observed side by side. If we ignore, for the moment, the septicemia and death of the animals, and concentrate exclusively on the skin, cortisone again becomes the miracle drug of the advertisements—for instead of the angry, reddened swellings which occur in normal rabbits, the skin remains flat, healthy-looking and flawless. And if we treat the animals with large doses of penicillin a day or so after the infection, the septicemia is readily controlled and the animals survive. The end result, under

these circumstances, is a dermatologic triumph for cortisone. Without penicillin, however, the apparently beneficial effect on the skin reaction can turn itself, overnight, into a local disaster. We have observed several cortisone-treated rabbits which remained alive for five days after infection, with no evidence of skin involvement, and then suddenly developed widespread lesions of hemorrhagic necrosis extending into skin areas far beyond the original infected area.

Such experiments illustrate, in exaggerated form, the charms and perils of cortisone and ACTH in certain human infectious diseases. The local reaction to infection, which sometimes constitutes the disease itself, can be suppressed to give the illusion of a curative effect. At the same time, the infecting agent is allowed to spread wherever its inclinations may lead it, unless stopped by appropriate antibiotic therapy. If the antibiotic is an effective one for the agent involved, the cure will seem complete. If not, the final outcome may be overwhelmingly in favor of the bacterium.

It is a curious paradox that adrenal insufficiency also causes a great increase in susceptibility to bacterial infection, which is quite comparable to that produced by cortisone. The most reasonable explanation, although admittedly an evasive one, is that two separate mechanisms are involved. Robinson[10] has reported an illuminating set of experiments on this problem, which provide clear-cut evidence that cortisone may, in special circumstances, be of great benefit in infection. He showed that adrenalectomized animals were rapidly overwhelmed when injected with pneumococci, and their resistance was restored to normal by small doses of cortisone. By increasing the dosage of cortisone he found that the mark could easily be overshot, and the resistance to infection again disappeared. Thus he obtained three groups of animals, in which the complexity of the role of the adrenal cortex in infection is nicely illustrated. At either end were the adrenalectomized animals with no resistance, one group with adrenal insufficiency and the other with cortisone overdosage. The third group, delicately and precariously balance in the center, were the animals receiving just the amount of cortisone needed to replace the normal functions of the adrenal, but no more than this amount.

While there is no question about the capacity of cortisone to interfere with natural resistance to infection, it is interesting that it has very little effect on acquired, immunological resistance. As an example, two

groups of twenty rabbits were treated with cortisone and then infected with Type I, Group A hemolytic streptococci. One group had received, one month previously, a subcutaneous injection of living Type I organisms. In the control group, all developed septicemia and died, while only six of the immunized animals had positive blood cultures and only three died. Such observations are inconsistent with the opinion, based on the demonstrated inhibition of antibody formation, that the action of cortisone on infection is due to interference with conventional immunological protective mechanisms.

In addition to its effects on the proliferation of bacteria in infection, cortisone has a remarkable action on the response to the most ubiquitous of bacterial toxic products, the endotoxins of gram-negative bacteria.[6, 11] Here, as in the case of streptococcal infection, it is possible to demonstrate two opposite effects of cortisone, one altogether good and the other wholly bad, side by side.

The endotoxins constitute a fairly homogeneous class of toxic substances which can be extracted from virtually all species of gram-negative bacteria but do not appear to exist in gram-positive organisms. The scope of their biological properties is indicated by the various names which have been attached to them by investigators in different fields. They are known to clinicians as "bacterial pyrogens" or as "shock-producing toxins", since they are the source of the reactions to contaminated transfusion or infusion fluids. To others they are known as "tumor necrotizing toxins", or, since they are the toxins which cause the Shwartzman reaction, as "Shwartzman-active toxins".

The experiments to be described, in which the opposing effects of cortisone are illustrated, were performed with endotoxins derived from meningococci, Sh. dysenteriae, S. marcescens, and E. coli.

First of all, the beneficial action of cortisone. When rabbits are given an intravenous injection of endotoxin, a certain proportion of them go into a state of shock and die within a few hours. The incidence of death is largely determined by the age of the animals. Young, growing rabbits are highly resistant to the material, while mature rabbits are extremely vulnerable. In order to test the action of cortisone on this kind of response, therefore, large animals must be used. The results are nearly always gratifying. A single injection of 5 or 10 mg. of cortisone prior to the injection of endotoxin completely eliminates the toxic effect.[12] None of the animals become sick or die, even when given very large

doses of endotoxin. It is perhaps this kind of action which is involved in the reported effects of cortisone on the shock-like state in human patients with overwhelming infections by gram-negative bacteria.

The coin, however, must be inspected on both sides. What is the effect of cortisone in younger rabbits, in whom endotoxin seems to produce no ill effects when injected by vein? We can best illustrate this by describing a typical experiment. Twenty young rabbits, weighing between 1 and 1.5 kilos, were injected with 10 mg. of cortisone each day for three days. On the third day, each was given an intravenous injection of meningococcal endotoxin. At the same time, twenty control, untreated rabbits received the same injection of endotoxin. The dose of endotoxin was large enough so that some of the control rabbits became visibly ill for a few hours, but none died.

During the next twelve hours there was little to choose between the two groups, except that the cortisone-treated animals were somewhat more active. After about eighteen hours, however, a sharp difference appeared. The control animals had now recovered completely, but the cortisone-treated group had become obviously ill and some were beginning to die. At the end of thirty hours the experiment was terminated and all were sacrificed. The control animals showed no gross or microscopic lesions in any of the organs, but in 75 per cent of the cortisone group, the kidneys showed the characteristic gross lesion of bilateral cortical necrosis.

Histological studies of the development of this lesion have revealed a good deal of information as to its pathogenesis. The earliest change, which occurs within the first few hours after endotoxin, is the occlusion of the glomerular capillaries by eosinophilic, homogeneous material which resembles fibrin—or, more closely, "fibrinoid".[11] It reacts strongly with the Hotchkiss-MacManus modification of the Schiff reaction, suggesting the possible presence of carbohydrate. It stains a yellowish-brown with phosphotungstic acid hematoxylin. In fresh, unstained suspensions of glomeruli, the capillary loops appear filled with a colorless substance, and in polarized light this material is found to be extremely birefringent. The birefringence is not affected by lipid solvents, but disappears promptly after exposure to trypsin or papain, indicating the presence of a protein substance with highly organized molecular structure.

It is the deposition of this material in the glomerular capillaries which

leads to bilateral cortical necrosis of the kidneys in cortisone-treated rabbits, following an injection of endotoxin. The event can be completely prevented by the administration of heparin at the time of injection of endotoxin,[11] which suggests, among other possibilities, that a disorder of blood coagulation may be involved. We have observed that a change occurs in the properties of fibrinogen after an injection of endotoxin,[13] so that flocculent precipitates of fibrinogen are produced in vitro by heparin as well as by other acidic polymers of large molecular size. In the living animal, at the time when "fibrinoid" material is being deposited in the capillaries, we found that the blood fibrinogen suddenly falls to extremely low levels. We suggest, tentatively, that the intracapillary material is derived from an altered, possibly polymerized form of fibrinogen.

The kidney is only one of many organs in which lesions are produced by endotoxin in cortisone-treated rabbits. Necrotizing lesions resembling hemorrhagic infarcts are commonly seen in the liver, spleen and lungs. The coronary arteries of the heart show segmental lesions of necrosis and fibrinoid deposition, and masses of fibrinoid are also embedded in the mitral and aortic valves.

All of these lesions are identical to those which characterize the so-called generalized Shwartzman reaction,[14-16] which is also produced by gram-negative bacterial endotoxin. In order to produce this reaction in normal animals, without cortisone, it is necessary to give two intravenous injections of endotoxin, spaced twenty-four hours apart. The fact that the same lesions occur in cortisone-treated rabbits after a single injection of endotoxin reveals an enlightening possibility concerning the mechanism by which cortisone may act. There is reason to believe that the reticuloendothelial system is in some way concerned with the defense of animals against this class of endotoxins. When colloidal materials, which are considered to interfere with the functioning of this system, such as thorotrast, trypan blue or colloidal iron saccharate, are injected by vein prior to a single injection of endotoxin, renal cortical necrosis and the other vascular lesions observed in cortisone-treated animals occur with regularity.[6, 17, 18] These colloidal "blockading" substances have also been found to produce a greatly increased susceptibility to infection by streptococci and other bacteria, resembling the effect of cortisone. Also, like cortisone, they prevent the appearance of local inflammatory reactions at the site of skin infection by streptococci at

the same time that systemic infection is enhanced. These and related observations have persuaded us to the view that the effects of cortisone on the process of infection may be mediated through the reticuloendothelial system. The reduction in size of the spleen and lymph nodes which occurs during cortisone treatment would be consistent with this hypothesis.

Having entered upon the subject of the mechanism of action of cortisone, we must at this point acknowledge the existence of other points of view. It has been suggested that the effect of cortisone is due to its demonstrated capacities 1) to impede antibody formation, or 2) to interfere with local inflammatory reactions, or 3) to prevent reflex vasomotor reactions to irritating stimuli, or 4) to delay the movement of colloidal and particulate materials through the ground substance, or 5) to alter the permeability of small blood vessels. There are valid experimental grounds to support each of these ideas, but they share, in common with our own view regarding the reticuloendothelial system, an absence of conclusive data which might settle the problem.

Kass and Finland,[8] Robinson[10] and others have studied the effects of other adrenal corticoid substances on infection. Compound F appears to have the same effect as cortisone. Compound B caused a very slight degree of enhancement in experimental pneumococcal infections. We have been unable to demonstrate any effect of desoxycorticosterone, combined with augmented salt intake, on the susceptibility to infection in rabbits. Selye and his associates[19] have stated that the enhancing effect of cortisone can be blocked by simultaneous injections of pituitary growth hormone. The experimental model which they employed involved the occurrence of spontaneous pseudo-tuberculosis infections in cortisone-treated rats; they observed that the incidence of such infection was lower in animals given growth hormone. In our laboratory, however, we have been unable to detect any effect of growth hormone on the susceptibility to streptococcal infection in cortisone-treated rabbits.

The Use of Cortisone and ACTH in Human Infections

We come now to the problems which confront the clinician concerned with the management of infectious diseases, who must determine the circumstances under which cortisone or ACTH should be used. It is in his tradition to make his decision on the basis of two classes of

information. The first is what he has observed, or others have observed, in other human patients treated with these hormones. The second is the information provided by the pharmacologists, physiologists, microbiologists and experimental pathologists. But when he attempts to utilize this information he finds himself surrounded by contradictory voices, some saying, "Yes" and others, flatly, "No".

His dilemma is, I think, best expressed by the following generalization: Cortisone and ACTH are always capable of causing at least two effects, one good and one bad, and it is necessary to weigh the one carefully against the other. A close inspection of the data available in animal experiments may help in the decision. In the presence of a bacterial infection, uncontrolled or uncontrollable by antibiotics, there is no circumstance in which the use of the hormones can reasonably be justified at the present time, with the exception of genuine adrenal insufficiency. If the infection can be completely checked, and if there are good reasons for hormone administration, they can perhaps be used with safety after the infection has been controlled.

Similarly, in situations where the endotoxins of gram-negative bacteria are involved in the disease—and this may be the case in such diseases as meningococcemia, typhoid fever, and brucellosis, the clinician must make a choice. And here, there is a further piece of information from animal experiments which may be of much importance, concerning dosage and time. The early, shock-like lethal reactions to endotoxin in animals can be prevented by a single injection of cortisone immediately before exposure to endotoxin.[12] Indeed, as Spink and his coworkers[20] have shown, the lethal effect in mice is prevented when cortisone is given an hour or so after endotoxin. The production of bilateral cortical necrosis of the kidneys by endotoxin and cortisone requires that the animals be *pretreated* with cortisone for two or three days before the injection of endotoxin.[11] It is possible, therefore, that the use of cortisone may be justified, in some circumstances, if it is given only for a short period of time, and only with the intention of alleviating shock. But to embark on a prolonged course of therapy, or to attempt to pretreat infants with meningococcemia in order to prevent the Waterhouse-Friederichsen syndrome, would seem to be courting hazard. In the latter regard, I am not thinking of the immediate hazard of such spectacular renal or arterial lesions as we have seen in the rabbit. These, if they occur at all in cortisone-treated human beings, must be exceed-

ingly uncommon. But we should be concerned, I think, about the possibility of later, long-delayed effects on the kidneys and blood vessels, resulting from minor, unrecognizable degrees of the same sort of lesion.

The management of typhoid fever provides a good illustration of the problem. At the present time, the majority of patients with typhoid respond well and promptly to chloramphenicol. In some, however, there may occur a severe reaction with vasomotor collapse, sometimes resulting in death, during the early stage of treatment, and it has been suggested that this is due to release of endotoxin from destroyed typhoid bacilli. Such reactions have been shown by Smadel and his associates[21] to be preventable by the administration of cortisone or ACTH at the time when antibiotic therapy is begun. No untoward reactions or evidence of renal injury were observed in any of the patients. The doses of cortisone were not large, and the period of treatment required was brief—at the most two or three days.

Comparable results were obtained by Spink and his associates[22] in the treatment of acute brucellosis. Cortisone or ACTH caused a dramatic abeyance of the toxic symptoms of the disease, and permitted the administration of antibiotics without untoward secondary reactions. Here again, large doses of cortisone were not required and a brief period of treatment was effective.

The reported effects of cortisone in typhoid fever and brucellosis indicate that despite the theoretical hazards involved, substantial benefit can be achieved. This does not mean, however, that the routine use of cortisone is warranted in all patients with these diseases. Until more has been learned about the final outcome, in long-term follow-up studies, it would seem more prudent to reserve hormone therapy for patients in whom a reaction of vasomotor collapse is considered to represent a threat to life. It should not be used to provide a greater degree of comfort for a few days in patients who may be expected to recover with antibiotic treatment alone.

The same can be said for the management of meningococcemia in young infants and children. On the basis of past experience, most of these patients will do extraordinarily well with prompt sulfadiazine treatment and the usual supportive measures. In a few instances, progressive shock occurs in spite of treatment, or shock develops before sulfadiazine can be given. In such cases the use of cortisone or ACTH,

as life-saving measures, may be justified. It should be emphasized, however, that if the hormones are going to work at all they will do so within a short period of time, and the period of treatment should be kept as short as possible. Above all, the beneficial effects of cortisone on the reaction of shock in meningococcemia should not be taken to mean that all aspects of this disease will be similarly benefited. As we have seen in experimental animals with meningococcal endotoxin, the effect may be quite the contrary.

The infectious diseases in which cortisone and ACTH are contraindicated require no detailed consideration here, and there is general agreement on the subject. Tuberculosis is an outstanding example, and the situation is analogous to that in the rabbit with experimental streptococcal infection—striking degrees of improvement may occur, temporarily, in localized lesions, but widespread dissemination of the infection is the unreasonable price to be paid for such benefit until completely effective antibacterial agents become available. The same can be expected in other varieties of bacterial infection in which antibiotic therapy is inadequate or unpredictable, notably in staphylococcus infections. Subacute bacterial endocarditis is another conspicuous hazard on two counts: it may be mistaken for acute rheumatic fever and treated with hormones, or it may occur as the result of cortisone in patients with chronic rheumatic fever who are under prolonged hormone treatment. In either case the continuation of cortisone can be expected to bring nothing but harm to the patient.

It has become increasingly obvious that patients undergoing hormone therapy must be observed closely for evidences of infection and these may be difficult or even impossible to recognize by their clinical manifestations. Cortisone not only permits infection to occur; it masks the evidence of infection. Frequent blood cultures are the easiest and most reliable means of avoiding or recognizing danger, and the lives of many patients have been saved by the discovery of septicemia at a time when things still seemed to be going reasonably well. Prophylactic antibiotic treatment is, of course, advisable during hormone administration, especially when prolonged courses are to be given. But frequent blood cultures are still mandatory to detect septicemias caused by microorganisms resistant to the usual antibiotics.

In conclusion, a final comment of a very general sort: The vast majority of clinical reports dealing with ACTH and cortisone have

concentrated on the successes of the agents in the face of great odds, and therefore deal to a large extent with the happy endings. Now, at the end of five years or so of experience, we have little information about the possible damaging effects of treatment, except for artificial situations involving experimental animals and occasional instances of fatal septicemia or vascular thrombosis in human beings. This may mean either that the human situation is an extremely fortunate one, with mostly good reactions and few bad ones, or that we have been concentrating our attention too closely on the bright side of things. We are in need, at this stage of events, of a more objective collection of information. As an example, it has been reported that some of the manifestations of periarteritis nodosa and lupus erythematosus occur in patients with rheumatoid arthritis after the cessation of treatment with large doses of cortisone.[23] I have recently seen two patients in whom cortisone was administered for what appeared to be minor degrees of chronic rheumatoid arthritis of long standing; both developed the classical picture of periarteritis nodosa within less than a month and died. Two other patients developed unrecognized disseminated sepsis during treatment with cortisone and subsequently died, and at autopsy both showed glomerular thrombosis and tubular necrosis similar to the lesions which we have encountered in the kidneys of cortisone-treated rabbits following endotoxin. It is difficult to interpret isolated, fragmentary observations such as these. It is conceivable that they are based on chance, or that they simply represent instances in which cortisone has had no effect on the progress of disease. But the alternative explanation, which is that cortisone may actually cause an enhancement of tissue damage or may allow new kinds of damage to occur, does deserve some consideration. A central clearing-house for such material, which would review not only the evident untoward results of treatment, but also the instances of apparent failure of treatment, would be a valuable institution for the next five years' experience with hormone therapy.

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THE COMPLICATIONS OF ANTIBIOTIC THERAPY*

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THE development of the antimicrobial drugs has brought into the realm of treatable disease the vast bulk of the bacterial infections which, as short a time as fifteen years ago, were responsible for considerable human illness and death. The remarkable therapeutic and prophylactic accomplishments of these agents have exceeded, in many instances, the expectations of even the most optimistic. In the light of the rapid control of many infectious processes by chemotherapy, it is easy to appreciate the enthusiasm which greets each new agent as it appears and to understand the haste to use it in any suspected infection. This phase of uncontrolled and uncritical hyperenthusiasm which is characteristic for every new antibiotic usually lasts until enough experience has accumulated to allow a proper evaluation. It requires a year or more, as a rule, before the "chemotherapeutic coin" reveals itself as having two faces. The side which deservedly attracts attention first and which is studied with greatest enthusiasm is bright and gleaming with the promise of the near-panacea; the other side is less attractive, considerably more somber in appearance and detracts, in varying degree, from the glitter of the coin as a whole.

The bright side of the coin has been examined extensively and the literature abounds with reports of the beneficial effects of all of the usable antimicrobial agents. These have been discussed many times and at a great length. In this paper, this side of the coin will not be examined but attention will be fastened rather on the one which is less attractive, so that some of the difficulties which arise when various antibacterial drugs are exhibited may be reviewed.

It is obvious that, although a great many of the perplexing and troublesome problems in infectious disease have been solved, many

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new and even more perplexing ones have been created. Among these are the complications that follow the administration of antibiotics. The list of undesirable effects is long and varied. Not all have occurred with each of the chemotherapeutic substances and some have been noted with only one or another of them. The incidence of individual reactions varies widely among different agents and with any one of them. There seems little doubt, however, that the total number of such reactions is increasing. The reasons for this are mainly three: 1) The increase in the number of available drugs, each of which may produce complications; 2) the rapidly increasing number of people who are being treated so that, even if the incidence of untoward effects for any specific agent remained constant, the total number of reactions would be increased; and 3) repeated administration of more than one drug leads to a greater risk of untoward effects as a result of exposure to hypersensitization to multiple agents.[1]

For the purposes of this discussion, the complications of antibiotic therapy have been classified into three groups, on the basis of the mechanisms involved in their production. First, there are those which are due to sensitization. These vary in severity from mild skin rashes which do not influence the course of the primary disease to situations which are life-threatening. The second group is related to the toxic and irritating effects of the drugs and includes irritation of the gastrointestinal tract, local reactions at sites of injection, toxic depression of bone marrow and direct injury to nerves. The third category encompasses those reactions which have their basis in chemotherapeutically-induced biological alterations in either the infecting organism or in the host which lead to the development of metabolic defects, superinfection, drug-resistance and depression of immune responses.

Reactions Due to Hypersensitization (Table I)

Reactions due to hypersensitization are among the most common of the untoward sequelae that follow the use of practically all of the antibiotic agents. They usually occur after ten to twelve days of treatment. They may appear in the absence of previous exposure to a drug or promptly after the administration of the first dose; this is particularly true of penicillin. Although elimination of the antibiotic usually results in rapid disappearance of the allergic manifestations, they may persist for one to two weeks or longer after therapy has been stopped. In some

TABLE I.—COMPLICATIONS OF ANTIBIOTIC THERAPY

Reactions Due to Sensitization
Morbilliform, scarlatiniform, urticarial, vesicular, bullous and purpuric rashes
Contact dermatitis
Erythema multiforme
Exfoliative dermatitis
Fever
Glossitis
Stomatitis
Cheilosis
Asthmatic breathing
Arthus reaction
Angioneurotic edema
Serum sickness
Anaphylactoid reactions
Eosinophilia
?Polyarteritis nodosa
?Disseminated lupus erythematosus

instances, the reaction is mild and disappears even while administration of the chemotherapeutic agent is continued. In others, it is of serious import and necessitates immediate cessation of treatment. In a few cases, it is necessary to interdict the use of the offending agent at some later time, because of the risk of death.

Untoward reactions to antimicrobial agents occur most commonly in the skin and are due, for the most part, to sensitization; they are often accompanied by fever and pruritus. Morbilliform rashes are the most frequent but scarlatiniform, urticarial, vesicular or bullous eruptions may also be observed. These are of relatively minor importance unless they progress to more serious lesions. Their development may not necessitate cessation of therapy or contraindicate the use of the provoking drug later in the patient's life. Contact dermatitis may follow exposure to many of the antibiotic agents; it has been observed frequently in pharmacists, physicians and nurses who handle streptomycin or penicillin, even though they may have never received either of these agents orally or parenterally. In addition to edema, vesicle formation or eczema of the hands and face, rhinitis and asthmatic breathing may be present. Contact dermatitis frequently results from the ill-advised application to the skin of antibiotics in suspension or solution in fat or

oil vehicles. The incidence of local and systemic allergic reactions following such treatment is higher than that which occurs when the agents are given by any other route and this type of therapy should be avoided, wherever possible. Among the more serious skin reactions to antimicrobial drugs are purpura, exudative erythema multiforme and exfoliative dermatitis. These have been observed most often after the use of penicillin, streptomycin, and chloramphenicol. Although purpuric lesions may be secondary to thrombocytopenia, they are present most often without an accompanying platelet deficiency. This does not, however, decrease the importance of this lesion, because its development may indicate a serious degree of vascular injury. In some cases, the purpuric eruption is a component of generalized serum sickness. Erythema multiforme exsudativum has been observed most commonly with the sulfonamides; it occurs rarely, however, with the other antibacterial agents and may be extensive, of the vesiculo-bullous type, and produce severe constitutional reactions. The most serious skin lesion which results from the administration of antibiotics is exfoliative dermatitis. This is very often of severe degree, extremely incapacitating and may be fatal, unless promptly and properly treated; its appearance necessitates immediate cessation of chemotherapy.

In the management of allergic skin reactions, the most important single procedure is discontinuation of chemotherapy whenever possible. With the present availability of a number of antimicrobial agents several of which may be effective against a specific organism, a change in therapy can frequently be made without seriously compromising the outcome of an infectious disease. The antihistaminic drugs may be helpful, particularly in combating pruritus; occasionally they reduce the severity of the lesions or limit their spread. ACTH and cortisone may be beneficial and are sometimes lifesaving in exfoliative dermatitis or in extensive and severe urticarial or bullous eruptions. These hormones also relieve the pruritus and edema, but they have not proved very helpful either in the prevention or limitation of most of the other lesions of the skin. The advisability of ACTH or cortisone therapy must be evaluated in relation to the state of activity of the infectious process because of the tendency of these agents to favor the persistence or spread of infection.

"Drug fever" may be the only manifestation of sensitization to an antibiotic or may precede or accompany other reactions. The rate of disappearance of the fever after treatment has been stopped is directly

related to the speed with which the causative drug is excreted. Fever tends to recur if the agent which first provoked it is given again.

Although many of the disturbances which occur in the mouth are due to irritative and toxic effects of the antibacterial agents, some are the result of sensitization. Oral complications of chemotherapy are observed most often following the use of the so-called "broad-spectrum" antibiotics,—Aureomycin (chlortetracycline), Terramycin (oxytetracycline), and chloramphenicol. A common lesion is ulcerative or vesicular stomatitis. This is characterized by dryness, burning, soreness, itching, redness and vesicle formation in the buccal mucous membrane; the tongue is red, smooth, shiny and swollen. Angular stomatitis has been ascribed to drug-induced riboflavin deficiency but it is probably due to an allergic reaction, since the administration of large doses of this vitamin fail to cure it. Black or brown furring of the tongue follows changes in the oral microbial flora with increase in yeast-like organisms. Such fungi are not always present, however, and it has been suggested that the discoloration may be due to sensitization. Although lesions of the mouth may occur after the systemic administration of antibiotics, they are observed most frequently when local therapy, in the form of lozenges or troches, is used.

The most serious allergic complications which follow the exhibition of antibiotic agents, especially penicillin and streptomycin, are the Arthus reaction, angioneurotic edema, serum sickness and anaphylaxis. Local edema, inflammation and occasionally necrosis, which increases in intensity with successive injections unless therapy is stopped, resemble the Arthus phenomenon. In the most severe cases, extensive sloughing of skin and muscle may occur. Angioneurotic edema of the lips, tongue, face and periorbital tissues, not infrequently accompanied by asthmatic breathing, has been noted after injection, inhalation or other exposure to antimicrobial agents. Typical "serum sickness" has been observed following sensitization to penicillin, and less often to streptomycin administered parenterally. The repository types of penicillin, especially those suspended in oil, are most often involved. The clinical picture varies in severity from mild fever, rash and leukopenia to one in which severe arthralgia, purpura, lymphadenopathy, splenomegaly, electrocardiographic changes, edema, albuminuria and hematuria in various combinations may be present. The reaction usually appears after chemotherapy has been given for one week or longer; the first manifestations may be

delayed, however, until a week or two after treatment has been stopped.

Reports of acute anaphylactoid reactions to antibiotics, some of them fatal, have been appearing with increasing frequency during the past year. In a recent study of this problem in ninety-five large general hospitals with a capacity of 51,000 beds, Welch and his colleagues[2] of the Food and Drug Administration discovered sixty-three anaphylactoid episodes, twenty of them fatal, which followed the administration of antimicrobial agents; none of these had been reported in the medical literature previously. Fifty-five of the cases followed the injection of procaine penicillin, one resulted from the administration of penthamate (Neo-Penil), two were produced by penicillin O, and one by oral Bicillin (dibenzylethylenediamine dipenicillin G). The remaining cases were due to the intramuscular or intrathecal exhibition of streptomycin. Of the twenty deaths, eighteen resulted from the injection of procaine penicillin, one from the intrathecal use of streptomycin and one from the oral ingestion of Bicillin. Welch and his co-workers also described twenty-five cases, five of them fatal, of anaphylactoid reaction to penthamate (Neo-Penil) which had been reported to the Food and Drug Administration.

Oral preparations of penicillin were found to be less likely to cause anaphylactoid reactions than the injectable forms. Very striking was the absence of this phenomenon with the administration of aqueous sodium or potassium salts of penicillin G, Aureomycin (chlortetracycline), Terramycin (oxytetracycline), chloramphenicol, bacitracin, polymyxin or neomycin. The individuals most prone to develop anaphylaxis are those who have a history of asthma, hay fever or other allergies. Although such reactions are relatively uncommon, they constitute a calculated risk in the use of drugs like procaine penicillin. Patients who have experienced anaphylactoid episodes should never again be exposed to the offending agent, unless this is absolutely unavoidable. Even a skin test with the drug or attempts at desensitization may be very dangerous and should not be carried out unless a physician is in attendance to detect and treat the acute asthmatic and vascular reactions which may develop.

Another phenomenon which has been ascribed to sensitization to antibiotics is eosinophilia. This may be present as an isolated finding or be associated with other allergic manifestations. Although the sulfonamides were the first antimicrobial agents to be incriminated in the pathogenesis of polyarteritis nodosa and disseminated lupus erythematosus, sensitiza-

tion to penicillin, streptomycin and other antibiotics has recently been suggested as one of the possible etiologic backgrounds of these diseases.

For the most part, hypersensitivity to an antibacterial drug is highly specific for the particular agent but, in certain cases, it may be elicited by closely related substances. Penicillin O produces a reaction in more than a third of the patients sensitive to penicillin G, and vice versa. Terramycin elicits a cross fixed reaction in individuals previously sensitized to Aureomycin. On the other hand, dihydrostreptomycin may be given to most but not all persons who have previously developed hypersensitivity to streptomycin, and vice versa.

The prognosis in cases of sensitization to antimicrobial agents is variable and often unpredictable. Many patients, especially those who have had fever and rashes following the use of penicillin and who have been considered sensitive to the drug, have subsequently tolerated treatment with this agent without untoward effects. This may be due to differences in the form of the drug employed in the first and in the later treatment and has been particularly true when sensitization has been the result of a repository type of preparation such as procaine penicillin, with or without aluminum monostearate, and purified salt of crystalline penicillin G was later used. Patch, endermal and conjunctival tests for sensitivity yield variable results which cannot always be correlated with the effects observed on subsequent administration of the agent. Attempts to desensitize individuals have been made and considered successful by some workers; however, such successes are open to the criticism that the patient may not actually have been seriously sensitized to the product used in the desensitization procedure or for subsequent treatment.

The antihistaminic drugs are of some value in the management of the acute delayed reactions of hypersensitivity; they sometimes give partial or complete relief from the pruritus associated with the skin lesions and may reduce the intensity or prevent the extension of the reaction but they do not affect the arthrosis or lymphadenopathy. ACTH or cortisone relieve the itching and joint pains; they have little or no effect on anaphylactic phenomena.

Toxic and Irritative Reactions (Table II)

Although they are at times difficult to separate from those related to sensitization, complications resulting from the direct irritating or toxic effects of various antibiotics are not uncommon. They are occasionally

TABLE II.—COMPLICATIONS OF ANTIBIOTIC THERAPY

Toxic and Irritative Reactions	
Albuminuria	Hepatitis
Hematuria	Depression of bone marrow
Cylindruria	Peripheral neuritis
Renal decompensation	Paresthesia
Stomatitis	Cerebral damage
Glossitis	Venous thrombosis
Nausea, vomiting	Pain at site of injection
Diarrhea	

due to the use of excessive quantities or concentrations of a drug. In some instances, however, the antibiotic is variably but inherently toxic to certain tissues. These reactions may produce severe discomfort and rarely death.

Serious toxic effects in the urinary tract have been observed following the administration of several of the antimicrobial drugs. Albuminuria and cylindruria are sometimes noted when streptomycin is administered, particularly when the urine is acid. A varying degree of renal decompensation may result from the administration of this drug, especially in individuals who have underlying kidney disease. The "broad-spectrum" antibiotics, Aureomycin (chlortetracycline), Terramycin (oxytetracycline), chloramphenicol, tetracycline (Achromycin, Tetracyn), penicillin and erythromycin have thus far been found to be generally non-injurious to the kidney. The less commonly used antimicrobial agents such as bacitracin, polymyxin and neomycin are nephrotoxic in some but not all patients. Their use may be accompanied by albuminuria, cylindruria, hematuria and reduction in renal function which may be progressive, particularly in those with prior kidney damage. These changes are usually reversible if they are detected early and treatment is stopped. Because of this potential toxicity, these antibiotics should be reserved for use in those situations in which serious infections have failed to respond to the administration of the less dangerous chemotherapeutic agents.

Toxic or irritative effects of antibiotic agents occur in any part of the gastrointestinal tract. Severe stomatitis and glossitis may be due to irritation produced by antimicrobial drugs applied locally in the form of lozenges or troches. Some question may be raised concerning the advis-

ability of this type of therapy, particularly because there is serious doubt that it is effective in eliminating infection. Disturbances in the function of the digestive tract are seen most often after the use of Aureomycin (chlortetracycline), Terramycin (oxytetracycline) and chloramphenicol. The ingestion of these agents may provoke a varying degree of nausea, vomiting and diarrhea which are probably due to direct irritation of the stomach and intestine; reduction in dose or administration of the antibiotic with milk or food frequently decreases the incidence and severity of the gastrointestinal symptoms. Penicillin and streptomycin given orally in comparable doses sometimes induce heartburn, nausea, vomiting and diarrhea. Tetracycline (Achromycin, Tetracyn) produces digestive difficulties less commonly than the other "broad-spectrum" drugs; these are also infrequent with erythromycin. Severe diarrhea with sanguino-purulent stools and marked constitutional reaction or shock following the use of antibiotics are usually due to acute enteritis, often staphylococcal, which results from superinfection.

The liver is occasionally affected by antimicrobial agents. Although hepatitis has followed the administration of streptomycin, it has not been determined definitely whether this was not "syringe hepatitis." Liver damage has been observed most often with Aureomycin (chlortetracycline) but also occurs, to a lesser extent, with chloramphenicol and Terramycin (oxytetracycline). Fatty changes in the hepatic cells have been noted after the use of excessive quantities of Aureomycin, particularly when it is given intravenously. They do not occur when doses of 1 to 2 gm. a day are administered orally to patients or normal human subjects. That the toxic effect is related to dosage is strongly suggested by the reports of the beneficial effects of Aureomycin in acute hepatic disorders in which necrosis is prominent. It is very difficult, in many instances, to determine to what extent dietary disturbances and infection are responsible either directly for the hepatic changes or indirectly in conditioning the reaction of the liver to the antibiotic.

Mild anemia, hypochromic or normochromic, has been noted following prolonged chemotherapy; this may be unrelated to therapy because it occurs frequently as a consequence of infection. The most serious blood disturbance produced by antibiotic agents is hypoplastic or aplastic anemia, which has occurred primarily in patients who have received prolonged or repeated courses of chloramphenicol in doses which have not been excessive. It has also been attributed to strepto-

mycin in at least two cases. A number of deaths have resulted from this complication; some have followed the treatment of trivial conditions. The bone marrow in these cases has revealed hypoplasia of all the elements; anemia, granulopenia and thrombopenia have characterized the peripheral blood. In most instances, the first sign of trouble is the development of granulopenia; early recognition of the decrease in neutrophils followed by immediate cessation of therapy practically always leads to recovery of bone marrow function. The necessity for carrying out frequent blood counts in patients receiving chloramphenicol is obvious and cannot be overemphasized.

Several of the antibiotics produce nervous system disturbances. The intramuscular administration of concentrated solutions of antimicrobial agents may lead to their accidental introduction into peripheral nerves and the development of a chemical neuritis which may persist for a long time. Paresthesias of the hands, tongue and circumoral areas have been caused by streptomycin but are particularly prominent with the use of polymyxin. The most frequent and serious of the neurologic disturbances provoked by antibiotic agents is damage to the eighth cranial nerve. The vestibular portion of the nerve is injured most often by streptomycin while dihydrostreptomycin and neomycin affect the cochlear portion. The frequency and severity of the damage are directly related to the total quantity and duration of therapy. It has recently been suggested that the combination of equal quantities of streptomycin and dihydrostreptomycin (the total dose being no greater than when either agent is used alone) is very effective in reducing the risk of auditory nerve injury.

Considerable attention has been focused on the untoward effects of the intraspinal administration of antibiotics, particularly streptomycin and penicillin. Marked increase in intracranial pressure, hyperirritability, twitching, convulsions and coma and death have been observed following the intrathecal instillation of these agents. In our clinic,[3] however, no complications of intraspinal chemotherapy have been noted in a large group of patients of varying age who have received even a large number of injections. It seems most likely that the majority of the severe reactions are the result of unintentional or accidental overdosage. The maximum quantity of penicillin which should be introduced intrathecally in adults in a single dose is 30,000 units and of streptomycin 100 mg. Smaller doses must be used in children. The observation of several other precau-

TABLE III.—COMPLICATIONS OF ANTIBIOTIC THERAPY

Reactions Resulting from Biologic Alterations in the Host and Infecting Agent
Negative nitrogen balance
Increased riboflavin excretion
Disturbance in electrolytes
Suppression of urobilinogen formation
Superinfection—bacterial and mycotic
Emergence of drug-resistant bacteria
Depression of immune response

tions aids in avoiding serious reactions: 1) The drug should be diluted in at least 10 ml. of physiologic saline; 2) the volume of spinal fluid withdrawn should be somewhat larger than that of the drug solution injected; and 3) the speed of injection should not exceed one ml. per minute.

One of the striking examples of the highly irritating action of antibiotics is the thrombosis of veins which results from the intravenous administration of such agents as Aureomycin (chlortetracycline). The pain and muscle tenderness which follow the injection of large quantities of crystalline penicillin G and of other antibiotics are also due to irritation. When applied in tissue cultures, in supravital preparations or in studies of tissue respiration, concentrated solutions of the various antimicrobial agents exert a direct toxic effect which produces cessation of cell growth, and inhibition of phagocytosis and of certain enzyme or other biochemical reactions. There is no conclusive evidence that any of the antibiotic agents, when given in the usual therapeutic doses, affects the coagulability of blood. One of the mechanical difficulties that arises from the use of insoluble preparations of antimicrobial drugs follows their occasional accidental intravenous injection, with the development of diffuse pulmonary thrombosis. Such reactions are sometimes confused with anaphylactic episodes.

BIOLOGIC ALTERATIONS IN THE HOST AND INFECTING AGENT (TABLE III)

Most of the antibiotic agents presently in clinical use are capable of producing biologic alterations in man and in the organisms which infect him. Some of these changes are of little consequence; others may seriously alter the course of the primary disease and occasionally may even be responsible for death.

Studies of the anti-metabolic effects of the antibiotic agents in human beings are few. Vitamin and other metabolic deficiencies have been described; many specific ones have been demonstrated in animals. In man, negative nitrogen balance and increase in riboflavin excretion result from the oral administration of moderate therapeutic doses of Aureomycin. Electrolyte disturbances occasionally accompany streptomycin therapy; they have been associated frequently with the use of viomycin, a tuberculostatic agent.

Uribilinogen may be absent from the urine and feces of patients during oral administration of Aureomycin (chlortetracycline) or Terramycin (oxytetracycline). This is probably due to suppression of the intestinal organisms responsible for the conversion of bilirubin to urobilinogen. Bilirubin is present, however, in abundance in the stools and in normal quantities in the serum. The recognition of this chemotherapeutically-induced artefact is important in the differential diagnosis of intrahepatic disease and obstructive lesions in the biliary system.

The administration of an effective antibiotic agent to a patient with an infectious disease, in addition to eliminating the causative organisms, produces a profound alteration in the composition of the bacterial population which normally inhabits certain tissues and organs. Such changes in microbial flora are most frequently of no clinical consequence, but occasionally are responsible for the superimposition of a serious infection on the one for which treatment was initially instituted. This is the phenomenon of superinfection which may be defined as the appearance of evidence (both bacteriologic and clinical) of a new infection at a time when the initial disease is responding clinically and bacteriologically to chemotherapy. Such secondary infections involve the respiratory tract, the colon, the genito-urinary tissues and the middle ear most frequently. Acute enteritis due to Staphylococcus aureus which follows the oral use of some of the so-called "broad-spectrum" antibiotics and which is occasionally fatal, is well-known. Preparation of the bowel for surgery by the administration of various antibiotics, often given in combination, may lead to pseudomembranous colitis which is often associated with an overgrowth of Proteus and Pseudomonas in the intestine. The development of secondary lung infection during the treatment of bacterial or viral pneumonitis is not uncommon, particularly in young children. Chronic infection of the urinary tract which is responding to treatment may relapse while the drug is still being given; in such instances, bac-

TABLE IV.—DURATION OF CHEMOTHERAPY IN RELATION TO INCIDENCE OF SUPERINFECTION

Duration of Chemotherapy Before First Appearance of Superinfection	*No. of Cases*
Days	
2	6
3	7
4	18
5	12
6	7
7	7
8	6
9	2
10	2
12	1

TABLE V.—RELATION OF AGE TO INCIDENCE OF SUPERINFECTION

Disease	*No. of Cases*	*Age-Yrs.*	*Total No. of Patients*	*Superinfections*	
				Number	*Percentage*
Pneumonia	369	1–3	201	14	6.96
		4–75	168	4	2.36
Otitis Media	257	1–3	103	11	10.67
		4–75	154	3	1.95

TABLE VI.—SUPERINFECTION IN RELATION TO PRIMARY DISEASE

Primary Disease	*No. of Patients Treated*	*Superinfection*	
		Number	*Percentage*
Pneumonia	369	18	5.16
Otitis Media	257	14	5.45
Syphilis	150	1	0.66
Diphtheria	424	3	0.71
Pertussis	80	16	20.0
Pharyngitis	1202	4	0.33
Meningitis	117	2	1.71
Tracheobronchitis	69	2	2.90
Poliomyelitis (bulbar)	20	3	15.0
Measles	9	3	33.0
Burns	1	1	—
Tularemia	1	1	—

teriologic study usually reveals an organism different from the one for which therapy was initially instituted and which is usually resistant to the antibiotic first applied. Among the complications occurring during chemotherapy, is an overgrowth of yeasts and fungi in areas like the mouth, pharynx and intestinal tract. This is observed following the use of all of the antibiotic agents but especially the "broad-spectrum" drugs. Mere increase in number of these organisms does not indicate, however, the presence of a superinfection. Kligman[4] has recently questioned the significance of yeasts in lesions of the oropharynx and lung which appear during the administration of antimicrobial agents. On the other hand, there are many clinicians who are of the opinion that localized mycotic infections may occur during the course of antimicrobial therapy. In some cases, diffuse fungus infection develops, the central nervous system, kidneys and other viscera are invaded, and death results; cultures of organs at autopsy in these instances reveal the fungi. There is, at present, no effective treatment for disseminated mycosis.

Although the problem of superinfection has been recognized for a long time, it has always been considered to be an uncommon and even rare phenomenon, and very little has been known concerning the factors which predispose to its development. A recent study in our clinic, of 3095 patients who had received one or another antibiotic agent,[5] revealed the incidence of superinfection to be 2.19 per cent; this is approximately the same as the incidence of skin eruptions with penicillin, and makes superinfection a relatively common complication of chemotherapy. Secondary infections most often involved the tissue which was the original site of disease, although other organs were occasionally affected. They appeared most frequently about four to five days after antimicrobial therapy was instituted (Table IV). The individuals most susceptible to superinfection were those who were less than three years of age (Table V), those whose primary disease was in the lungs (Table VI), and those who received drugs with a relatively "broad" antimicrobial effect, particularly combinations of agents (Table VII). In most cases, more than one factor was involved; the more numerous the predisposing situations in a patient, the greater was the risk of secondary disease. Antibiotic-produced infections occasionally convert a benign and self-limited disease into a serious, prolonged or even fatal one. This is, in part, due to the fact that the responsible organisms, Proteus, Pseudomonas, drug insensitive staphylococci and yeasts for example, are

TABLE VII.—INFLUENCE OF TYPE OF CHEMOTHERAPY ON SUPERINFECTION

Drug	*Total No. of Patients Treated*	*Superinfection*	
		Number	*Percentage*
Penicillin	2538	37	1.46
Penicillin and streptomycin	172	8	4.65
Streptomycin	31	4	12.92
Chlortetracycline	95	7	7.35
Oxytetracycline	31	4	12.92
Chloramphenicol	46	7	15.2
Streptomycin and chlortetracycline	2	1	50.0

not susceptible or are totally resistant to the available antibiotic agents.

Abscesses sometimes develop at the site of injection of antibiotics. They are usually due to organisms resistant to the drug which produced them. E. coli, P. vulgaris and Cl. perfringens (B. welchii) have been isolated from such lesions. The source of these bacteria may be the skin, the antibiotic, or improperly sterilized needles and syringes.

Potentially one of the most serious complications of the widespread use of antibiotics is the emergence and increase in prevalence of organisms resistant to most or all of the available antimicrobial agents. Many recent reports have stressed the importance of this problem, particularly in relation to Staphylococcus aureus. While 75 to 85 per cent of strains of this organism were sensitive to penicillin ten years ago, approximately the same percentage is at present resistant to this agent. Lack of drug-sensitivity in the Staphylococcus is not limited to penicillin; it is also becoming increasingly prominent with Aureomycin (chlortetracycline), Terramycin (oxytetracycline), chloramphenicol, tetracycline and erythromycin. It must be pointed out, however, that the marked increase in antibiotic-insensitive staphylococci is most prominent in hospitalized patients. In the general population, the incidence of penicillin-resistant strains is only about 10 per cent. The Staphylococcus is not the only organism which has become insusceptible to antibiotics. Many of the gram-negative bacteria responsible for urinary tract infections, E. coli, Ps. pyocyaneus, A. aerogenes and Proteus vulgaris, for example, are developing decreased sensitivity to various chemotherapeutic agents and infections due to them are becoming increasingly more difficult to man-

age. The phenomenon of emergence of drug resistance is not common to all bacteria or all antibiotic agents. It is a fortunate circumstance indeed that, despite their long exposure, the organisms responsible for some of the common infectious diseases have remained highly susceptible to antimicrobial drugs. There are, for example, no authenticated strains of penicillin-resistant Pneumococcus, Gonococcus or beta-hemolytic Streptococcus.

An important alteration in the response of the host to infection which is produced by the use of antibiotics is depression of the formation of antibodies to various organisms and their products. Several observers[6-10] have demonstrated that prompt and intensive penicillin therapy of acute streptococcal infections of the respiratory tract inhibits the elaboration of antistreptolysin, antistreptokinase and type-specific antibacterial antibody. In pneumococcal infections in man, on the other hand, penicillin treatment produces no detectable alteration in the serologic response.[11] In rats, mice and rabbits, the exhibition of penicillin early in the course of experimental pneumococcal infection has been shown to suppress antibody production.[12,13] The use of Aureomycin (chlortetracycline), Terramycin (oxytetracycline) or chloramphenicol in scrub typhus produces no appreciable effect on the eventual height of the titer of OX-K antibodies. However, if treatment is started early in the disease, the appearance of agglutinins may be somewhat delayed.[14] The mechanism of depression of antibody formation is thought to be related to the speed with which the antimicrobial drugs eliminate infecting organisms from the host and in this way do not allow stimulation of the immune reaction. That this is probably the mechanism involved is suggested by the observation that delay in treatment results in the development of the expected quantity of antibody. It has been postulated, however, that some of the antibiotics may have a direct effect on antibody elaboration without relation to persistence of antigen since the administration of penicillin, dihydydrostreptomycin and Terramycin (oxytetracycline) appears to depress the primary immune response to bovine gamma globulin labeled with radioactive iodine.[15]

A Patient With Multiple Complications of Antibiotic Therapy

Although it is no longer unusual for many individuals to exhibit one or another of the complications of antibiotic therapy, the appearance of several of them in the same person, especially when they convert a

minor illness into one which almost terminates fatally, is unusual and merits special attention and comment. The following case illustrates the difficulties and dangers which arise when a patient develops, almost simultaneously, reactions due to toxicity, hypersensitization and superinfection.

A sixty-two year old woman developed dysuria, urinary frequency and gross hematuria. Intravenous pyelogram revealed no renal lesion. After one week of treatment with Furadantin without improvement, she was given one gram of Terramycin per day; this led to the rapid disappearance of symptoms. However, diarrhea, consisting of watery stools every two to four hours, first appeared on the sixth day of antibiotic therapy. Nevertheless, the drug was continued for several days until the intestinal difficulty became so severe that the patient was sent to a hospital. Here, she was found to have fever, marked dehydration and severe abdominal pain. The stools were completely liquid and contained blood. Bacteriological studies revealed Ps. pyocyaneus bacteremia; this organism and Proteus were the only bacteria cultivated from the feces. The white blood count was normal but there was a considerable degree of anemia. Since the Pseudomonas was sensitive to chloramphenicol, one gram of this drug and 2 grams of Gantrisin (sulfisoxazole) per day were administered. Two transfusions were given. Diarrhea, high fever, severe abdominal pain and anemia persisted, however, and a cough productive of purulent sputum appeared. After six days, the patient was transferred to another hospital. On admission here, she had a temperature of 102.8°F., a blood pressure of 116/60 and appeared moribund. There was slight icterus of the sclerae. The lungs revealed dullness to percussion and fine inspiratory rales over the entire lower lobe. The abdomen was markedly distended, bowel sounds were low pitched and infrequent, and there was an extreme degree of generalized abdominal tenderness. There were 9 gm. of hemoglobin per 100 ml.; the white blood count was 1100 with only 18 per cent neutrophiles. Several blood cultures were sterile. The stools contained blood and pus; the only organisms recovered were Ps. pyocyaneus and P. vulgaris. Roentgenogram of the chest demonstrated consolidation of the lower lobe of the right lung. Ps. pyocyaneus was isolated in pure culture from the sputum.

Because Pseudomonas was apparently responsible for the pneumonia, polymyxin was administered in a dose of 40 mg. intramuscularly and 100 mg. orally every six hours. Crystalline penicillin G was given parenterally in an attempt to prevent superinfection with gram-positive bacteria. No improvement in the clinical condition occurred in the next three days; at this time, the strain of Pseudomonas isolated from the lungs was found to be sensitive only to neomycin. For this reason, polymyxin was withdrawn and 2 gm. of neomycin injected intramuscularly daily, in divided doses. During the next two weeks, during which neomycin was administered, the temperature returned to normal, the pneumonia cleared, the diarrhea stopped and there was marked improvement in the general clinical condition. Despite the administration of numerous blood transfusions, mild anemia persisted and the white blood count remained between 1000 and 1500 with about 20 to 30 per cent neutrophiles during the first week. Following this, there was a gradual increase in the total number of white blood cells and neutrophils; normal levels were reached about three weeks after admission. About the sixth day in the hospital a generalized, pruritic, maculopapular rash developed, but disappeared gradually despite the maintenance of therapy. After about one week of neomycin treatment, the patient complained of tinnitus and difficulty in hearing; these became more marked during the following week. She was observed for ten days after cessation of all treatment and left the hospital completely well except for an auditory deficit of about 50 per cent.

An analysis of this case reveals six complications of chemotherapy; diarrhea, bacteremia, pneumonia, depression of the bone marrow, dermatitis and deafness. An attempt to reconstruct the series of events, as they occurred, suggests that the Terramycin used in the treatment of the cystitis produced pseudomembranous colitis, a condition in which Pseudomonas and Proteus are often the predominant or only organisms in the stool flora. This superinfection of the bowel was then followed by bacteremia with deposition of organisms in the lung, producing a Ps. pyocyaneus pneumonia. The marked granulopenia was probably the result of depression of the bone marrow by chloramphenicol or Gantrisin or both and probably contributed to the development of the bacteremia and pneumonia. The skin rash which developed when neomycin and penicillin were being given may have been due to either of these agents. The involvement of the ear was most likely the result of injury of the eighth cranial nerve by neomycin.

Discussion

To limit the inspection of the "chemotherapeutic coin" to the unattractive side alone is just as misleading and unrevealing of the truth as to view only the face which gleams with the picture of the benefits to be derived. In order to determine the true value of the entire coin, it becomes imperative, therefore, to examine both sides carefully and to reach a conclusion only after each has been evaluated in terms of the other and in proper relation to the whole. So, only through long experience and unbiased, critical evaluation of the good and the bad in antibiotic therapy can an intelligent understanding of its real benefits and limitations be reached. I will have failed miserably indeed if what I have said leaves the impression that the drugs which have been discussed are only harmful, or that their dangers outweigh the benefits to be derived from their proper use. To act on such an impression would mean the loss of countless lives and the permitting of untold suffering and pain.

The fact that harmful effects may follow the use of antibiotic substances must never discourage the physician from the use of any of them in any situation in which they are definitely indicated. It should, however, make him very careful in their use when they are required, and very cautious and hesitant about employing them in instances in which indications for their application are either entirely lacking or, at most, only slightly suggestive. To do otherwise is to run the risk, at times, of

converting a simple, benign and self-limited disease into one which may be serious or even fatal. The physician must always be mindful of the fact that the use of any powerful therapeutic agent is always accompanied by a calculated risk. The antibiotics are no different; to condemn them on the grounds of their potential dangers is no less unrealistic and unwise than to accept them as universally applicable, completely beneficial and entirely harmless.

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PIROGOFF IN THE CRIMEAN CAMPAIGN 1854-1855*

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New York

THE Crimean Campaign, fought one hundred years ago between Russia and a coalition of France, England and Turkey, was but an episode in the war which took place on the Balkan peninsula. Victorious in the Balkans, the coalition transferred hostilities to Russian territory, concentrating its forces on the fortress of Sebastopol (or Sevastopol) in the Crimea which it besieged from March 1854 to July 1856. Historians are not in full accord as to the reasons for the conflict, but they all agree that like other wars, it caused enormous suffering, was a sheer waste and settled nothing.

Many episodes of the bloody encounter still haunt historians. The tragic fate of the British Light Brigade, immortalized by Alfred, Lord Tennyson in his poem *The Charge of the Light Brigade*, was recently recounted brilliantly by Cecil Woodham-Smith,[1] and the epic of Florence Nightingale has been detailed in more than one recent memoir.

The medical and sanitary conditions that prevailed in the armies of the coalition received considerable attention in the French and British literature at the time of the conflict and have often been discussed in subsequent years, but those in the Russian Army were only meagerly recorded. Strict censorship by the authoritarian regime of Nicholas I (1825-1855) and disregard for human life were probably the chief reasons for this neglect. Then too, the army was composed mainly of serfs (one third of the Russian population was in bondage) who in time of peace were looked on as beasts of burden and in time of war as so much cannon fodder.

Since Russia fought on her own soil, while the bases of the coalition were remote, it would be reasonable to assume that the medical conditions of the Russian Army were superior. In the pages to follow, the medical status of the Russian Army will be described as seen by the

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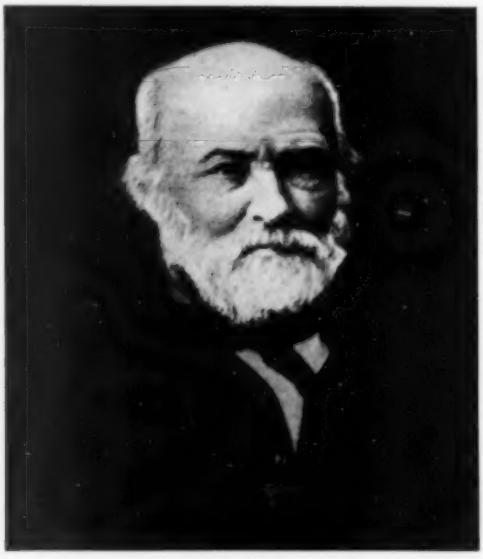

NIKOLAI IVANOVICH PIROGOFF — 1810-1881

well known surgeon Nikolai Ivanovich Pirogoff who recorded his observations in letters to his wife.* The correspondence was published after Pirogoff's death and was never translated into a foreign language. It represents an interesting chapter in the history of war medicine. It also reveals Pirogoff as a man to those outside his native land who have known him as a surgeon only. "*Celui qui fait du bien*", wrote the French philosopher, "*est de tous les pays, et il à droit a un laissez-passer universelle.*"

Biographic Sketch: Pirogoff was born in 1810, the youngest son of a Moscow civil servant who brought up his large family in accordance with the strict rites of the Russian Orthodox Church. After a rudimentary schooling, terminated in 1824 when he was fourteen,

* It is interesting to note that thirty American physicians from various parts of the United States participated in the campaign. They were in Paris, engaged in postgraduate work, when they were hired by agents of the Russian government. A Russian author stated that these physicians went to the Crimea inspired by the anti-British sentiment that existed in America at that time, and attracted, too, by high salaries. It is most likely, however, that the ambitious young doctors were eager to acquire experience under war conditions. Shortly after their arrival in the Crimea, they all succumbed to typhus or cholera, which caused far more extensive suffering in both armies than did the actual bullets. No mention of the presence of these American physicians can be found in Pirogoff's writings.

Pirogoff matriculated as a student of medicine at the University of Moscow. He was aided by Dr. Mukhin, Professor of Anatomy and physiology, who was the Pirogoff family physician; Professor Mukhin had been appointed to his position at the University from the rank of Feldsher in the army.

Pirogoff relates that Professor Mukhin was too shy to lecture on the female reproductive organs. The lecture coincided with Lent and he would say: "Since the subject is rather 'meaty' we shall postpone it to a more suitable time," but that time never came. This went on year after year. Another teacher, Dr. Moudrov, Professor of internal medicine, taught students that in cases of typhus where medicinal herbs were ineffective, the patient should be advised to make a pilgrimage to the Ikon of the Holy Mother of Iversk, which remedy, he was certain, would not fail. "It is impossible to imagine", wrote Pirogoff in his memoirs, "the ridiculous conditions which prevailed in the university. We boys, fourteen to seventeen years of age, attended lectures, not infrequently, merely for fun."

The amount of medical knowledge acquired by Pirogoff during his three years' study in school can easily be conjectured. He was graduated in 1827, at the age of seventeen, and by sheer luck (again through the influence of the family physician, Prof. Mukhin) was sent abroad for postgraduate work in order that he might ultimately take up a teaching position in his Alma Mater. The University of Dorpat (founded in 1798) where he was assigned was thoroughly German although the province of Esthonia, conquered by Peter the Great in 1710, was a part of the Russian Empire. The university was one of the best equipped of that period; it kept close contact with Western Europe and was fully informed on scientific progress throughout the world.

Pirogoff was greatly impressed by the little town. "No", he wrote home, "this is not Moscow; there is more freedom here. All are equal in public places. Servants and state employees are on an equal footing and have the same privileges. The Rector of the University dominates the city, and the professors together with the students rule it."

Pirogoff chose surgery as his specialty, and was attached to the surgical clinic whose chief, Prof. Moier (a pupil of the Italian surgeon Scarpa), was an educated and highly cultured man. Pirogoff soon became acquainted with the French and English medical world represented by Bichat, Broussais, Astley Cooper, Abernethy and John Hunter.

His Thesis *Uber die Möglichkeit der Unterbindung der Aorta abdominalis* was inspired by similar studies carried out in England and America. Since there was not enough work in the small clinic to keep him busy he devoted himself to anatomy, and during the four years of his stay in Dorpat he excelled in this study.

In 1833, at the age of twenty-three, he was sent to Germany to continue his studies. "On my arrival in Germany", he wrote, "I found medicine to be totally isolated from its main realistic foundations—anatomy and physiology. Surgery did not concern itself with anatomy and the leading surgeons, Rust, Graefe, and Diffenbach had superficial if any knowledge of the subject. . . . It is difficult to imagine [he wrote] how little interest German physicians of the time displayed in fundamental pathologic processes . . . Pyemia was not understood by German surgeons. Throughout my sojourn in Berlin I heard no word of purulent infection. I gained my first knowledge of this condition from the Frenchman Cruveilhier [Jean Cruveilhier, 1791-1874]."

He attached himself to the Charité Hospital, which he called "*eine reine Mordgrube*" (a graveyard), a reservoir of filth and putrid infection. For one Thaler he was given permission to utilize a corpse for an operation, and for 15 Silbergroschen to ligate vessels. Several hundred corpses were bought at this reasonable price from Frau Vogelsang (a technician performing the autopsies).

On his return to Dorpat in 1835 his chief, Moier, relinquished the Chair of Surgery because of his appointment to the position of Rector of the University. Pirogoff was then called to take the place of his former chief.

The six years of his professorship at Dorpat passed uneventfully. The surgical clinic of 20 beds, half vacant under his predecessor, was now occupied with patients coming from town and country. However, his interest in anatomy did not diminish. While in Dorpat he completed and published his *Anatomia chirurgica truncorum arterialium atque fasciarum fibrosarum autore, 1837-1838*, and a monograph *Ueber die Durchschneidung der Achillessehne, als operative-orthopedisches Heilmittel (Ztschr. f. Med. 16:*441, 1840).

After six years the provincial university began finally to irk him and he decided to return to Moscow where he was promised the chair of surgery. Through nepotism, however, and obscure influences an

inferior man was appointed to the chair. Pirogoff was named professor of surgery at the Medico-Chirurgical Academy in St. Petersburg and Surgeon to the Voenno-Soukhopoutny Hospital, a colossal institution of more than one thousand beds, a "*Mordgrube*" like the Charité. In accepting the appointment he wrote to the Minister of his intentions to "ennoble the hospital by transforming it into a safe place for the sufferer and into a Temple of Science." He met, however, a hostile opposition from an inept, ignorant and corrupt administration and visiting medical staff. A feud ensued which bore all the traits of a struggle between two ideologies, East and West, with no quarter given. The techniques of "big lie" and "smear" were freely used. A mercenary newspaper man was hired to blackmail him in the press; patients were bribed and instructed to complain that he performed surgical operations on them against their wishes; employees were paid for spying on him and reporting his alleged misconduct. An attempt was finally made to declare him insane. Indeed, Pirogoff and his opponents represented two worlds that spoke different languages; two elements—oil and water —that were in no way miscible. His stay in the Academy was a ceaseless struggle. But it did not deter him from hospital and teaching duties, private practice, and scientific pursuits. His capacity for work was prodigious. In 1843 his *Complete Course of Applied Anatomy of the Human Body* appeared, and in 1846 he brought out his famous five volume *Anatomia topographica sectionibus per corpus humanum congelatum triplice directione ductis illustrata.* In 1847 he published his *Recherches pratiques et physiologiques sur l'etherisation,* clinical and experimental studies on rectal anesthesia which he was the first to introduce and to apply successfully in surgery and obstetrics. His monograph *Anatomie pathologique du cholera morbus, avec un atlas, XVI planches colorées,* was published in 1849 and in 1853 he published his monograph on the osteoplastic (Pirogoff) operation. *Der Gipskleberverband, Elastic Plaster-of-Paris Cast in Simple and Compound Bone Fractures as Applied in the Transport of Wounded on the Battlefield* appeared in 1854.

In spite of his reputation and scientific accomplishments the struggle with the passing years grew in intensity. In addition, his rivals became jealous of his success in private practice. In the early fifties his position in the Voenno-Soukhopoutny Hospital became intolerable, virtually untenable. On his resignation from this institution he addressed the Medical Board as follows: "I became convinced on many occasions

that you rely on the opinion of ignoramuses; on those who are behind the times and hate everything that is beyond their limited understanding. You accept the opinion of those to whom the hospital is merely a soldiers' barracks, the patients annoying subjects, and chloroform and surgical instruments too expensive for hospital economy. Is it possible for one with sense, with honest intentions, with integrity, with devotion to science, to remain a consultant in a hospital degraded by the ignorance of the Physician-in-Chief. . . ."

At this juncture the armies of the coalition set foot on the Crimean peninsula and besieged the port of Sebastopol. Pirogoff, forty-four years old and the only great surgeon of Russia, failed to get a commission. And when spurred by patriotism he applied for one, his application was ignored. A commission was finally given him through the intervention of a Duchess, a friend of his wife. He was appointed Consultant Surgeon and Head of a Special Unit of Female Nurses.

The first impression from the front was recorded by him as follows: "I shall never forget the day of my arrival in besieged Sebastopol in November 1854. The entire road from Bak-chi-Sarai, for 30 versts was blocked with transports carrying wounded, war supplies and provisions. It was pouring. The sick and the wounded, including the amputated, lay in twos or threes in peasant carts moaning and shivering from cold. Men and animals alike moved in mud knee deep. Carcasses were scattered everywhere. Swollen and cracked bellies of oxen and horses protruded from pools of muddy water. . . . One could hear the moaning of the wounded, the cawing of birds of prey and the echo of thundering cannon from Sebastopol. . . ."

Letters to his Wife: Pirogoff's letters to his wife, from the battlefield, paint an indelible picture of many phases of the famous Crimean Campaign. They also reveal him as a man and as a physician Excerpts from the letters follow:

Sevastopol, November 14, 1854.

"Arrived in Sevastopol the 12th. Started to write you a detailed letter yesterday but had no time to complete it. From 8 in the morning to 6 in the evening I remained in the hospital where rivers of blood were flowing. . . . Over 4000 wounded. . . . One hears the explosion of bombs and shells. So much to do that there is no time to think of letters to one's family. Travel on horseback to hospitals and back home covered with blood, sweat and mud."

Sevastopol, November 24-28, 1854.

"What happened October 24 [the battle of Inkerman] was not unexpected; it had been foreseen; it was inevitable. Ten, even more—eleven thousand men dropped out of line; over six thousand wounded. And for these wounded nothing was prepared. Like dogs they were thrown on the ground. For weeks they remained without attention and virtually without food. . . . Arrived in Sevastopol, November 12, eighteen days after the 'affair' and found over two thousand wounded huddled on filthy quilts soaked in blood. Labored for ten days from dawn to dusk to sort them and to separate those who needed urgent operations. Many should have been operated upon shortly after battle. . . . Linen and means of transportation were not prepared in advance, and when, to the six thousand, more wounded were added there was utter confusion. . . ."

Simpheropol, November 29, 1854.

"The life I am leading here is not conducive to loneliness, and though I do not see you and the children I am not lonely. My thoughts are wholly with the wounded—wounds—you see them in your sleep, you see them on waking. . . .

"It is impossible to relate what we found in Bak-chi-Sarai. Bitter want, Slavic heedlessness, medical ignorance and Mongol untidiness—all combined in enormous proportions. . . . Three hundred and fifty wounded placed close to each other in two small military barracks; men with filthy, stinking wounds lying near those whose wounds are clean—all in hermetically shut and overheated compartments."

Bak-chi-Sarai, December 13, 1854.

"The sick are badly treated here. The transport is horrible—in open carts; the men lack warm clothes, spend nights in the fields or in unheated *izbas* [peasants' huts] . . . then cross the Dniepr in canoes."

These are excerpts from the Sevastopol Letters written by Pirogoff to his wife. They were not intended for publication. Pirogoff hoped they would be read to a highly placed person, the Grand Duchess Elena Pavlovna, a friend of his wife, who might be helpful in ameliorating this deplorable state of affairs. Pirogoff failed to visualize that the disease was systemic and could not be palliated by a Duchess.

War Medicine: It is remarkable that although war is as old as man, war medicine is of comparatively recent origin. Throughout the ages, kings, generals, or bandits, in charge of armed forces used to provide their own persons or their close entourage with what they thought to be expert medical help, while the armies were usually abandoned to themselves. Sick and wounded soldiers were left on the battlefield, on the road, in towns or villages where they died of their wounds, exposure or starvation. Monasteries and charitable individuals accommodated but a few. Swarms of charlatans and fakirs followed armies selling balms, herbs, and amulets to the sick and the wounded. They usually robbed their credulous clients of their hard earned cash and of their loot. Women, a usual accompaniment of mercenary armies, often flocked to the battlefield when the fight was over and afforded medical care, consisting chiefly in sucking the wounds, a procedure practiced since time immemorial (*La démoiselle suçait la plaie de son damoiseau*).

The invention of gun powder and the introduction of firearms in the 15th century* brought changes in the technique of mutual destruction, and this led gradually to the training of "specialists" in the treatment of the new type of wounds. Still, military medicine did not exist until the beginning of the 17th century when Henry IV (1598-1610) built a military hospital and provided the army with what were then called surgeons. Progress was made under his successor, Louis XIII (1610-1643) when the famous Cardinal Richelieu developed the medical branch of the army by building so-called sedentary hospitals and training military surgeons. Greater advances were made under Louis XIV (1643-1715) whose military medical organization was copied by Frederick the Great. As no surgeons were available in Germany, Frederick "borrowed" the medical personnel from France.

Army surgeons in those years were usually stationed far behind the fighting forces and the wounded used to be carried to them from the front lines. Conditions changed under Napoleon, when surgeons were often available on the battlefield. The names of Percy** and Larrey*** Chief Surgeons in Napoleon's armies, are well known. The French speak of them as "fearless soldiers, irreproachable physicians" (*soldats sans*

* This century is notable for the discovery of at least three "civilizing" factors: Printing, Syphilis and Gunpowder.
** Percy, Pierre-François, 1754-1825.
*** Larrey (pronounced Larré), Dominique, 1766-1842.

peur médecins sans reproche). Larrey is said to have been the first to introduce in the army the so-called *Ambulances Volantes*–Flying Ambulances.

The erstwhile enthusiasm for the medical organization under Napoleon vanished as a result of recent investigations. "When one coolly examines the immense work performed by Napoleon," wrote de Fourmestreau,[2] "one is forced to admit that in spite of Percy and Larrey, Horteloup and Desgenettes (the last two were physicians), the medical organization of the Imperial Armies was far from being on a par with that of the army proper. . . . One is stupefied at the primitive state of the sanitary conditions of the army of the Empire. . . . Once wounded a soldier was nearly always lost to the army. . . . When one peruses the memoirs of Percy and Larrey one is made painfully aware of the defects of the organization and the extravagant waste of manpower."

Fabre de Faurer, an officer in Napoleon's army, wrote in his memoirs: "At the end of the battle the field of Borodino* presented a frightful picture. Medical service was virtually absent. All villages and vacant houses in the vicinity were packed with wounded from both armies, in an utterly helpless condition. Endless fires raged in nearly all settlements situated in the zone occupied or passed by the French Army. Those wounded, who succeeded in escaping from fires, crawled in thousands along main roads seeking means to prolong their miserable existence."

It is well to remember that in Napoleon's day French Military Medicine led medicine throughout the continent. "Les étrangers eux mêmes," wrote Rochard,[3] "s'inclinaient alors devant notre superiorité. Partout ou nos confrères se trouvaient en rapport avec les médecins des armées ennemies, ceux-ci s'empressaient d'observer leur pratique et de leur demander des conseils. Les allemands surtout, qui en étaient encore à l'enfance de l'art, accouraient aux leçons de Larrey lorsqu'il les réunissait autour de lui dans les conférences pratiques." ("Foreigners bowed to our (French) superiority. Whenever enemy surgeons came in contact with ours they were eager to observe them working and plied them with questions. The Germans particularly, whose knowledge of medicine was still rudimentary, flocked to Larrey when he invited them to his conferences.")

* A village in Russia where a fierce battle occurred September 7, 1812, between the French under Napoleon and the Russians led by Koutouzov.

If the most efficiently organized army of Napoleon displayed such medical chaos, medical conditions in other armies can only be conjectured. In Russia, according to Tarle, those who had been wounded near Witebsk at the beginning of July (1812) reached Viazma (150 miles away) about August 7, without even the most primitive medical assistance. Many of them arrived from Witebsk unbandaged, because there were only two doctors available. There was a complete shortage of medicines and bandages, and the worms (maggots) devoured the wounded alive.

Although nearly half a century had passed since the Napoleonic campaign, no appreciable change occurred in the state of military medicine.

"Maybe our enemies also are affected by the same trouble—God willing", Pirogoff hoped. In this respect, God was "willing". The armies of the coalition, too, suffered from "bitter want, medical ignorance and Mongol untidiness". The state of medicine and sanitation too, was inadequate in the opposing camp. "Let's hope", prayed Pirogoff, "that the cursed ways of the heathen, who looked upon man as a blind strategic weapon and did not care about the aftermath of war and public welfare, will receive a deadly blow here as well as in the countries fighting against us."

When Pirogoff complained to the Commander-in-Chief, Prince Menshikov (whom he branded "jester at the Court") about the suffering of the men, the "cold and uncharitable" prince smiled and said: "In the past it was worse." Possibly so, but not much worse. The High Command of that period "loved" the soldier only when healthy. A sick or wounded soldier was looked upon as "breakage", "waste", which should be thrown overboard. Pirogoff branded this attitude as the cursed ways of the heathen against which he fought with every ounce of his great energy.

In Sevastopol as in the Voenno-Soukhopoutny Hospital and in the Medico-Chirurgical Academy in St. Petersburg, he came in contact with an incompetent medical organization and with corruption. "Always and everywhere in times of war or other catastrophies", he wrote, "there are individuals ready to sacrifice general public interest for personal advantages. It is not surprising, therefore, that abuses by the hospital administration are more frequent during hostilities. Pray, what purpose will a clever surgical intervention serve, or, for that matter

any other method of therapy, if the sick are exposed to conditions detrimental to their well being?" "It is the moral duty of the military physician", he continued, "to be vigilant in order to detect misconduct by the administration, for indifference is liable to lead to calamities more disastrous than medical and surgical mistakes. . . . Fear and narrow egotism should not keep the doctor from speaking out the truth and from revealing incompetence where the welfare of thousands is concerned. Old and young physicians should not lose sight of the fact that hospitals suffer more from inefficient administration than from epidemics."

By administration, Pirogoff meant the sanitary and medical organization of the army as a whole. He defined war as a "Traumatic Epidemic" which requires a host of competent physicians. According to him, in war as in great epidemics, the number of physicians, particularly capable ones, is never sufficient. In Pirogoff's estimation one physician should be allowed for every 107 men; and a Division of approximately 16,000 men should be provided with at least 77 physicians.

As a physician, Pirogoff lived the life of his patient. "In the soul of a hospitalized person", he wrote, "particularly that of a wounded soldier, new desires, new tendencies, new emotions and new prejudices develop which must be respected by the physician." Krupskaia, a nurse in the Crimean Campaign, wrote in her memoirs: "Nikolai Ivanovich [Pirogoff] worries about the sick and the wounded as a father worries about his children. His humanitarianism and selflessness are reflected in all of us. Patients feel better from his touch alone. He has become a legendary hero. The soldiers believe that he is able to perform miracles. Once a decapitated soldier was brought to the dispensary. The surgeon at the entrance called the attention of the stretcher bearers to the incongruous 'patient'. 'Nichevo, your Honor,' replied the men, 'the head follows. Gospodin (Mr.) Pirogoff will somehow attach it and our brother soldier still be of some use.'"

Si non é vero, e ben trovato. . . .

More Letters: Simpheropol, December 6, 1854.

"This letter is mailed to you by post. I mailed two letters to you from Sevastopol and one from Simpheropol by courier. One letter remains in my portfolio; I fear to mail it for it contains too much truth. . . . For Heaven's sake, my little soul, do not be lonely and do not com-

plain – it robs me of all desire to work. Be patient. I must finish what I have begun. It is impossible to abandon the undertaking before completion. Remember that we live on this earth not only to gratify personal ambitions. A great drama is unfolding, the results of which may be felt centuries hence. It is a sin to sit idly by as an onlooker. I am well aware that for those like ourselves who are blessed with a family, it is very difficult to abandon the agreeable and peaceful life and to submit to the trouble, deprivations and hardships of separation from the dear ones. But those who are not indifferent to the Sublime and the Holy cannot look at things one-sidedly, egotistically. And you, for whose feelings I have the greatest respect, will console yourself with the thought that your husband left you and the children, convinced that he labors not in vain. Arm yourself with patience and with faith in Holy Providence."

In the midst of this personal outburst, Pirogoff returns to his main theme:

"The most horrible thing is the lack of means of transportation, leading to constant accumulation of sick and wounded in different places where they remain deprived of quilts and linen. The transportation most commonly used is primitive cart on terrible roads, causing immense suffering. The smallest wound becomes complicated and the patient's sufferings increase. . . . In Simpheropol patients were placed in stables. There was no straw for quilts and the old putrid straw was soaked with urine and pus. . . . In open peasant carts, they carried the sick for seven hours from Simpheropol to Perekop. In the midst of these unfortunates who tolerate without complaint, what seems to be misery beyond human endurance, we thank God and reconcile ourselves to our own deprivations. . . . Such are the results of complacency and heedlessness. Nothing was prepared. They joked; they did not believe in the coming of the war."

Preparedness. It sounds almost contemporary. *Plus ça change, plus c'est la même chose.*

Sevastopol, April 29, 1855

". . . It is easy to say to oneself: Be silent, it is none of your business. But to hold one's tongue – that is impossible. Four hundred wounded were transported yesterday and thrown in tents where there was hardly

sitting space for that many. With amputated arms, with amputated legs, with fresh wounds, all on the ground or on miserable small quilts. It has been raining all day. What will happen to them? Tomorrow I shall know.

"Found the patients in mud like pigs. I will report to the Commander-in-Chief. Let them be angry. I care little. . . ."

Pirogoff was waging "war" on several fronts: He treated the sick and the wounded; he kept close watch on the corrupt hospital administration; and finally he labored on the improvement of evacuation and transportation of the sick and wounded from the battlefield.

Sorting of Wounded: He classified all wounded into four categories:

1. The hopeless, relegated to the care of priests and nurses.
2. Those who urgently required operations.
3. Those whose operations could be postponed for one or two days and who could be evacuated to a nearby hospital.
4. The slightly wounded who after dressing could be returned to their units.

Intelligent sorting evidently saved the lives of many and kept the fighting forces from depletion. Pirogoff opposed indiscriminate operations in the field. "Only life-saving operations such as arrest of hemorrhage should be performed in the field."

Classification of Wounds: The description and classification of wounds inflicted by firearms was based by surgeons of that period on clinical data only. The dynamics of the lesion and the various pathologic aspects of wounds were not sufficiently appreciated. All gunshot wounds were invariably opened and thoroughly investigated for the presence of a bullet or for debris. "Nothing was considered more urgent," wrote Pirogoff, "than the extraction of the bullet." The wounds were therefore sounded with probes and with the finger which had not even been washed. The opinion was prevalent that a radical exploration of the wound was a sine qua non in all gunshot wounds. With the technique used in those days, the procedure led to catastrophic results in most instances. Pirogoff related an example from his own practice. A private of athletic build was brought to his ward with a bullet in his thigh. In accordance with the accepted practice "I proceeded to extract the bullet, succeeding after two hours of labor. Next morning in

making rounds I found the bed of my athletic patient vacant. He had died during the night." He stressed the necessity of handling gunshot wounds with the utmost care. "I consider it my duty", he wrote, "to warn young surgeons to refrain from investigating gunshot wounds with their fingers; to refrain from attempting the forceful extraction of splinters, and generally to abstain from any insult to the wound."

Amputation has been a favored operation throughout the ages. The older surgeon was radical; he preferred amputation to conservative treatment in which he usually failed. Whether the amputation should be performed soon after the occurrence of the accident ("amputation immédiate") or postponed ("amputation tardive") was usually settled in favor of the former. Surgeons amputated legs lightheartedly without justification. This horrible practice was perpetuated to the days of Lister. Clapesattle[4] in the *The Doctors Mayo* depicted the situation in the following terms: "Amputate, amputate, amputate. For everything from the bite of a cat to the misdirection of a woodsman's axe. Persons with missing extremities must have been commonplace in the community. If a limb is diseased cut it off, was one of the oldest principles in surgery, and improvement had occurred only in the direction of greater neatness and dispatch. The technique was the thing, the surgeon most honored was the one who could dismember a limb in the fewest seconds." Pirogoff quoted an authority who stated: "Dass man durch versäumte Amputationen viel mehr Kranke verliert, als man Glieder rettet." (By postponing amputations more lives are lost than limbs saved.) "I too," said Pirogoff, "was influenced and guided by the apodictic tone of the teaching. As a young lecturer I taught my pupils that any patient with a fractured limb who refuses an amputation should be looked upon as a mad gambler." During the Caucasian conflict, in 1847, Pirogoff became convinced of the futility of indiscriminate amputations.

"There are no cures in rash, energetic and premature intervention in the field", he now insisted. "Die Amputation in Allgemeinen ist kein Preservativ-Mittel gegen den schädigen Einfluss einer Hospital-Konstitution," he reiterated. (In general, amputation is no safeguard against the noxious effect of "Hospital-Constitution.")

"Stromeyer says", wrote Pirogoff, 'amputation is imperative when neither leeches nor ice is available.' I say: An amputation should be

resorted to only when there is no plaster-of-paris and no means of applying a fixed plaster-of-paris cast. I observed favorable results in instances when the closed cast remained untouched for weeks; when it finally was removed the wound was healed and the fracture united. . . . I am decidedly in favor of complete rest and I am a staunch supporter of the conservative method of treatment of fractures." "The application of a plaster-of-paris cast," he stressed, "will enable transportation of a man with a broken limb and will also serve as a therapeutic measure. The immobilizing plaster-of-paris should be looked upon as the best method against infiltration and distention in fractures."*

Warm and charitable, cosmopolitan and patriotic, "every inch a gentleman" (this English expression was used by a well known Russian physician Shingarev to characterize Pirogoff), he fought relentlessly as man and as physician the "cursed ways of the heathen".

Sisters: Presently he acquired assistance that admirably fitted into his scheme.

"A group of Sisters arrived a few days ago and started to work with zeal," Pirogoff informed his wife. "They turned the hospital upside down, took care of food, drinks, distributed tea, wine—just marvelous. If this continues, if their fervor does not cool off, then our hospital will take on a new aspect."

It is well to remember that organized and sustained female nursing was inaugurated during the Crimean Campaign, when Sisters were employed not only in base hospitals but also in the field and in the bastions. The surgeon N. A. Veliaminov[5] wrote: "Jean Henry Dunant** admitted that Pirogoff was largely responsible for his visit to the battlefield, which ultimately resulted in the organization of the International Association of Private Voluntary Assistance in War." "Pirogoff's role in the matter of private assistance in war," continues Veliaminov, "is not only outstanding; it is unique. I dare say that in the history of private help in

* How he arrived at the idea of using the plaster-of-paris was described by him as follows: "About 18 months before the siege of Sevastopol I noticed for the first time in a sculptor's studio the effect of a mixture of plaster-of-paris on cloth. I surmised that it can be used in surgery and immediately applied a cloth soaked in a mixture of plaster in a compound fracture of the tibia. It was successful. The plaster became dry in a few minutes and the oblique fracture with considerable bloody extravasation and perforation of the skin healed without suppuration or other complications. I was convinced that this dressing may be used widely in military medicine. I described the method in order to make it accessible to everybody." The plaster-of-paris cast was applied by him successfully in Sevastopol.

**Dunant, the founder of the Red Cross, visited the battlefield of Solferino where the bloody encounter took place in July, 1859. The well known pamphlet *Souvenir de Solferino* was published by him in 1862; and the first meeting of the Geneva Conference occurred in 1864.

war, the name of Pirogoff may be placed on the same level with that of Dunant. Pirogoff was not only the originator of this humanitarian institution but also one of its builders; for a quarter of a century he was devoted to it with an unusual zeal, persistence and love."

Pirogoff left deeply touching sketches of some of his "Sisters". From the female nursing episode in the Crimea he drew far-reaching conclusions. "The results of the participation of women in the war prove at any rate", noted Pirogoff, "that up to now we totally ignored the admirable gifts of our women. These talents clearly demonstrate that the 'woman problem' had every right to be posed at the time of the Crimean Campaign. . . . Opponents of emancipation of women affirm that there are great differences between the sexes, such as the brain which is smaller in the female, etc. This should not be relied on; it holds no water. If a woman is brought up and educated properly she is just as capable as a man to adopt scientific, artistic and social culture. However, it is essential that she should not relinquish her 'womanhood' as a result of her new status."

In the Crimean desert of mud, sweat, blood and corruption, the nurses represented an oasis to which Pirogoff invariably turned for rest and assistance. He was as much "stunned" by the women in his hospital as the soldiers themselves. He spoke of them in almost every letter to his wife.

"The presence of neatly dressed women rendering assistance with sympathy and kindness enlivens the valley of suffering and misery. . . . We expect the arrival of the *Misericord Widows,* who will also be under my supervision. . . . Many are well educated. One nun, one novice, one officer's widow, and our own Lodé, who speaks five languages and whose duties are chiefly the care of wounded prisoners. Mme. Lodé told Dr. Djuliani that she is prepared to tolerate anything in her new position except *des choses indecentes.* So the considerate doctor covered the patients with sheets and blankets in her presence."

Of one of his Sisters he wrote: ". . . Bakunina took care of patients with tact and devotion. Her task was to see that the patient received the proper amount of food; that the linen was clean; that the straw in the quilts was regularly changed. She was an admirable executive and always got what she wanted. . . . In November, 1855, I asked her to take charge of a transport of wounded. Atmospheric conditions were horrible. In

big boots with a coarse peasant's sheepskin she followed on foot in the impassable mud of Perekop the *teleguas* [primitive four-wheeled carts] packed like sardines with sick and wounded; nights were spent in cold and humid *izbas*. She was an example of patience and industry. . . . Her entire personality breathed sincerity; her acts and her feelings were in complete harmony. . . . She seemed to be an amalgam of all that is sublime. . . . The more obstacles she met the more zeal and energy she displayed."

Khitrovo, another of the Sisters, was of a different grain. While Bakunina belonged to the rational, practical type, Khitrovo was rather a mystic. "The two sisters reminded me," wrote Pirogoff, "of Martha and Maria from the Gospel—both from the Little Flock of Christ, which is to say that He accepted the highly practical as well as the deeply religious. . . . Khitrovo belonged to those exceptional characters capable of blending the mystical religious with the practical. On one occasion she said to me: 'I pray with greater sincerity and with greater warmth in a poor village church listening to the simple and monotonous singing of the Deacon than in a luxurious Temple with a solemn set-up.' By her appearance and manners she seemed to me at first to be a sort of nun, but her education, her intelligence and her mystic religious trend were so conspicuously harmonious that the austere ascetism never showed up." She died of typhus during the Crimean Campaign.

A third Sister, Karzova, "was much younger and less experienced than Bakunina and Khitrovo. She was taciturn and quiet; tactful, sustained and independent in all her acts."

Pirogoff divided his nurses into three groups: Surgical Assistants, Housekeepers and Apothecaries.

"Each evening", he wrote to his wife, "Khitrovo and Karzova come to see me and scheme how to catch the hospital thieves. . . . Karzova is simply tireless. Spends days and nights in the hospital, cooks for the patients, changes dressings, does everything. In spite of all her efforts we did not succeed in finding out why the chicken soup prepared with ninety chickens for three hundred and sixty patients lacked the proper taste. When the Sisters do the cooking their soup tastes much better even when a smaller number of fowl is used. We even sealed the kettles, but to no avail. It is a pity: the amount assigned is such that one could feed the patients well, yet they get no nourishment at all."

Dr. S. P. Botkin, Pirogoff's assistant in the Crimean Campaign, wrote: "Our goal was to ascertain that a piece of meat or bread allotted to the sick soldier reached him before it shrank to its minimum. This was far from easy with that social group which considered state property a birthday party cake to be devoured by anyone who could lay hands on it. By order of Pirogoff every portion of meat was weighed when delivered in the kitchen. Kettles were sealed so that the contents could not be removed. Nevertheless our broth was a failure. They [the superintendents] found means even under such supervision of depriving the wounded of their portions."

Pirogoff's interest in the sick and wounded never ceased. "Those who think that I went to Sevastopol just to cut off legs and arms are grossly mistaken", he wrote; "I have done that before and in great numbers."

Closing Note: To the War Administration the man Pirogoff was something unheard of: a physician with civic consciousness; a physician who demanded humanitarian treatment of the sick and wounded. Lacking background, vision and humanitarianism the Administration could not and did not appreciate his ideas and efforts in the tragic Crimean Campaign.

His efforts likewise received no sympathy or support from the Medical Department to whom he was a kind of *enfant terrible*. In fact, he was intensely opposed.

With the war over, Pirogoff relinquished his teaching and hospital connections and assumed other duties which he discharged with his customary vigor and talent. The post-bellum period of his life is another chapter.

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SECTION ON MICROBIOLOGY*

*Abstracts of Papers***

Presented at the Meeting, December 15, 1954 at The New York Academy of Medicine

Selective Inhibition of Virus Multiplication by Synthetic Chemicals

IGOR TAMM

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Viruses multiply only inside cells. Therefore, to inhibit the synthesis of virus materials or the development of new virus particles, chemical agents need to act in the interior of host cells. This immediately raises the question of what effects such compounds have on the host cells themselves.

It is to be expected that selective inhibition of virus multiplication cannot be achieved with substances which inhibit the energy yielding mechanisms of cells, denature proteins, or in other ways cause extensive alterations in the normal functions of the cells at virus inhibitory concentrations. The effect of sodium malonate on the multiplication of influenza virus exemplifies non-selective action.[1] Malonate is a competitive inhibitor of succinic dehydrogenase; in the absence of a continuous supply of di- or tricarboxylic acids it blocks the whole Krebs cycle. In the presence of 0.02 to 0.06 M malonate, endogenous respiration is depressed and so is virus multiplication. The difficulty is, of course, that any activity of the cell that derives energy from the Krebs cycle would suffer in the presence of malonate.

It appears that, from the viewpoint of selective inhibition, compounds which inhibit certain biosynthetic mechanisms are of greater interest. Available evidence indicates that with special compounds it is possible to interfere with certain biosynthetic processes of cells infected with certain obligate intracellular parasites and to obtain a quantitatively differential response on the parts of the host and parasite. The selective inhibitory action of the so-called broad-spectrum antibiotics on the multiplication of agents of the psittacosis-lymphogranuloma group is well established. Evidence obtained from studies of bacterial metabolism[2-5] suggests that chloramphenicol and chlortetracycline act through inhibition of protein synthesis in the infected cells. They do not interfere with nucleic acid synthesis, at least not in bacteria. It should be emphasized that the term "selective inhibition" as used here does not imply that the processes or reactions affected are those required only by the parasite or that they play an insignificant role in normal cell physiology. On the contrary, it is likely that the processes inhibited by the broad-spectrum antibiotics are qualitatively common to host and parasite. In fact, at moderate concentrations the broad-spectrum antibiotics are capable of inhibiting host cell proliferation.[4] Although the precise mechanism of selective action is not understood, it is likely that factors such as sites and rates of biosynthesis in the infected cell, intracellular permeability barriers, and the precise nature and degree of dependence of intracellular parasite reproduction on host cell metabolism may be involved.

Although chloramphenicol and the tetracyclines inhibit the multiplication of intracellular agents of the psittacosis-lymphogranuloma group without causing serious damage to host cells, multiplication of agents of the size of vaccinia or any of the

* Thomas P. Magill, Chairman, Maclyn McCarty, Secretary.

** Manuscripts received February 1955.

smaller viruses is not thus affected. It is probable that the biosynthetic processes involved in the reproduction of the so-called "true viruses" are even more intimately linked to host cell metabolism than those of psittacosis and lymphogranuloma agents, at least on the level of protein synthesis.

As a working hypothesis, the idea is put forward that it may be possible to interfere with biosynthesis of virus nucleic acid in an infected cell without causing marked or irreversible alterations in the host cell nucleic acid metabolism or other metabolic activities. The results of studies with benzimidazole derivatives[6-7] indicate that selective inhibition of virus multiplication can be obtained with certain specially designed small molecular synthetic compounds.

The main part of the studies reported below was carried out with influenza B virus multiplying in the chicken chorioallantoic membrane maintained under rigorously controlled conditions in vitro. In some experiments, embryonated eggs and mice also were used. In addition, multiplication of mumps virus in eggs was studied. These studies have been carried out in collaboration with Drs. Karl Folkers and Clifford H. Shunk of the Research Laboratories of the Chemical Division of Merck and Company, Inc., who synthesized the compounds used.

Influenza virus in membrane culture was chosen mainly because it provides a particularly convenient system for quantitative studies on animal virus multiplication. In view of the diversity of nucleic acid composition of animal viruses, results obtained with influenza virus may not be applicable to certain other viruses. Recent evidence indicates that the main nucleic acid component of influenza virus is RNA.[8, 9] This circumstance emphasizes the desirability of studies along the line of structural analogs of nucleic acid building blocks or precursors containing ribose. On the other hand, it would seem that a reasonable approach to selective inhibition of vaccinia virus would require desoxyribosides, since this virus contains DNA.

The first compound employed in these studies on influenza virus multiplication in the chorioallantoic membrane was 2,5-dimethylbenzimidazole (designated MB). The structural similarity between MB and the benzimidazole moiety in vitamin B_{12}, i.e., 5,6-dimethylbenzimidazole, is obvious. Furthermore, the benzimidazole derivatives and the purine derivatives adenine and guanine have the same bicyclic skeleton with respect to size and a common imidazole ring.

Experiments showed that MB does inhibit influenza virus multiplication, but that the activity is low. Under precisely defined conditions, it was only 2.7 times more active, on a molar basis, than unsubstituted benzimidazole, which was adopted as the reference compound in these studies. The latter compound causes 75 per cent inhibition of Lee virus multiplication at a concentration of 0.0085 M or 0.41 mg/ml, and it has been arbitrarily assigned a relative inhibitory activity of 1.

In view of the fact that both the 5,6-dimethylbenzimidazole moiety in B_{12} and the adenine and guanine moieties in ribonucleic acids are linked to ribofuranose, it appeared fruitful to explore the ribofuranosyl derivative of MB. It was hoped that this derivative might show greater activity than the simple 2,5-dimethyl compound. However, it was found that the ribofuranosyl derivative of MB had no effect on virus multiplication at a concentration as high as 0.0035 M.

Two glycosides of the 5,6-dimethyl compound were also tested, and the results were similar. Both the lyxopyranosyl and ribofuranosyl derivatives failed to inhibit virus multiplication. Since the 5,6-dimethyl compound not containing a pentose does possess a low degree of inhibitory activity, just as does 2,5-dimethylbenzimidazole, it was concluded that conversion of these methyl benzimidazoles to glycosides eliminates inhibitory activity.

A different line of approach was therefore adopted. A series of chlorobenzimidazoles was explored, and it was found that simple chloro derivatives were more active than the corresponding methyl compounds. This was not unexpected, because similar findings have been made previously in other fields. Of greater interest was the finding that the ribofuranosyl derivative of 5,6-dichlorobenzimidazole was 7 times more active than the simple dichloro compound. Thus, depending on substituents present in the benzimidazole nucleus, substitution of ribofuranose

at N1 may make or mar inhibitory activity. 5,6-Dichloro-1-β-D-ribofuranosylbenzimidazole (designated DRB) was found to be 92 times more active, on a molar basis, than the reference compound, i.e., unsubstituted benzimidazole. DRB caused 75 per cent inhibition of Lee virus multiplication at a concentration of 38 millionths M or 12 μg/ml.

A comparison with MB showed that DRB was thirty-five times more active than the dimethyl derivative. The important question was whether there was any difference between these two compounds with regard to selectivity of action. For each compound, activity ratios were computed by comparing the virus inhibitory concentration with the concentrations at which diminution of O_2 uptake by the chorioallantoic membrane, macroscopically visible damage to the membrane, or retardation of cell proliferation in roller tube culture were observed. These ratios were found to be about 3 to 4-fold higher for DRB than for MB, indicating that increase in virus inhibitory activity was greater than increase in toxic properties. It may be emphasized that an activity ratio of 10.5 obtained with DRB in comparative studies on virus inhibition and inhibition of O_2 uptake is impressively high. With DRB no effect on O_2 uptake was observed at a concentration which caused more than 99.9 per cent inhibition of virus multiplication.

In single cycle experiments with Lee virus in the chorioallantoic membrane in vitro the latent period is approximately three to four hours. Both MB and DRB markedly prolong the latent period. To ascertain the time of action of these compounds in the multiplication cycle, experiments were carried out in which the interval between inoculation of virus and addition of the compounds was varied and the effect on multiplication determined. On the basis of kinetic evidence of two kinds obtained from such experiments, it is possible to distinguish between the modes of action of MB and DRB. First, those processes inhibitable by DRB are of shorter duration than those inhibited by MB. This is true for the production of both soluble C-F antigen and of virus particles. Secondly, with MB the duration of inhibitable processes is the same (five hours) both for soluble C-F antigen and virus synthesis. In contrast, with DRB the inhibitable processes are of shorter duration for the soluble C-F antigen (1.5 hours) than for virus particles (three hours). Thus, of the two compounds DRB is not only thirty-five times more active than MB, but its effect is more restricted in time. The combined evidence indicates that of the two substances DRB is considerably more selective in its action.

This conclusion is corroborated by the finding that DRB inhibits Lee virus multiplication in embryonated eggs and in mice without serious effects on the host, whereas MB fails to do so. DRB also causes marked inhibition of mumps virus multiplication in the chick embryo. The embryos which received DRB showed no obvious slackening of spontaneous activity, and no deaths attributable to DRB occurred. In similar experiments with MB inhibition of virus multiplication was not demonstrable except when the amounts of the compound used were sufficient to cause damage to or death of the hosts.

With this information on the selective action of DRB as a background, it is of interest to inquire into the relationship between chemical structure on the one hand and virus inhibitory activity and selectivity of action on the other. First the relationship between structure and virus inhibition will be considered. Comparison of 1-β-D-ribofuranosyl derivatives of benzimidazole containing 1 to 3 chloro substituents in the benzenoid ring shows that the activity of chlororibofuranosyl compounds increases as the number of chloro substituents in the benzenoid ring is increased. 1.6 μg of the most active compound, the trichloro derivative, TRB, suffices to cause 75 per cent inhibition of Lee virus multiplication. Comparison among representatives of a series of glycosides of 5,6-dichlorobenzimidazole reveals the profound effect of the nature of the glycosyl group with regard to virus inhibitory activity. When the glycosidic ring was changed from the 5-membered ribofuranoside to the 6-membered ribopyranoside, the inhibitory activity was lowered to 1/6th of that found for DRB; in fact, the activity of the ribopyranoside was almost identical

with the activity of the simple 5,6-dichloro compound. Substitution of an arabino or glucopyranosyl moiety for the ribofuranosyl moiety gave compounds of very low activity, lower than that of 5,6-dichlorobenzimidazole.

Thus, relative to virus inhibitory activity two important structural relationships have been established: high activity is a function of the presence of β-D-ribofuranose at N1 and the presence of unnatural substituents (Cl); in increasing number in the benzenoid ring.

In experiments on the relationship between structure and selectivity of action, macroscopic changes in the appearance of the membranes were used as an indication of toxicity. These changes, flaccidity and yellowish discoloration of membranes, correlate well with diminished O_2 uptake by the membranes. The great obstacle to such studies was the low solubility of the di- and trichloro compounds. Because of this, it has not been possible to compare the toxicity of 5,6-dichloro- or 4,5,6-trichlorobenzimidazole with that of the corresponding 1-β-D-ribofuranosides.

However, a comparison between 5-chlorobenzimidazole, the corresponding 1-β-D-ribofuranoside and MB was possible. These compounds were compared at an equivalent virus inhibitory concentration, namely 4 times the 75 per cent inhibitory concentration. Both MB and 5-chlorobenzimidazole caused the same degree of macroscopic damage to the membrane in vitro when used at equivalent virus inhibitory concentration. On a molar basis the 5-chloro compound was twice as active as the dimethyl derivative, both with respect to virus inhibition and production of tissue damage. 5-Chloro-1-β-D-ribofuranosylbenzimidazole, on the other hand, did not cause significant tissue damage when used at four times the 75 per cent inhibitory concentration. On a molar basis the ribofuranosyl derivative was three times more active as an inhibitor of virus multiplication than 5-chlorobenzimidazole. Thus, in this case there was a disproportionate increase in virus inhibitory activity relative to tissue damaging ability. With the methods used, these differences are highly significant. It is probable that the selective action of DRB, i.e., the dichloro-ribofuranosyl compound that was discussed above, is due to the fact that the ribofuranosyl group increases the virus inhibitory activity of the molecule without increasing toxic properties to the same extent.

Studies with benzimidazole derivatives indicated that both virus inhibitory activity and selectivity of action are quantitative properties that can be manipulated by synthesis of derivatives with modified chemical structure and biological activities. The importance of quantitative biological studies in guiding chemical synthesis should be underlined. Although the best compounds that have been made are not only highly active as inhibitors of influenza virus multiplication but also exhibit significant selectivity of action, further improvements may be possible. Clearly, β-D-ribofuranose at position N1 in the benzimidazole nucleus is desirable from the points of view of both high virus inhibitory activity and low toxicity. The chlorine substituents are very desirable from the point of view of high virus inhibitory activity but less so with regard to selective action. It should be possible to replace them with some other substituent with highly desirable properties on both counts.

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*Passive Cellular Transfer of Sensitivity to Serum**

MARY M. TREMAINE

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Passively induced sensitivity to serum antigens in rabbits was investigated by using a technique involving some features of both delayed and immediate sensitivities. Leukocytes were used as the transfer agent and the sensitization of cell donors involved an immediate system as to antigen and reaction.

Donor animals were sensitized by daily intracutaneous injection to the point of typical Arthus reactions with hemorrhage. Horse serum, beef serum and bovine serum albumin were used as antigens; none of these elicited reactions in normal animals in the amounts used. The cells used were restricted to those obtained in the peritoneum forty-eight hours after injection of mineral oil. Collection of cells occurred fifteen to twenty days after the beginning of sensitization.

Transfer of sensitivity occurred with each of three routes for injection of cells into normal recipients: subcutaneous, intraperitoneal and intravenous. Transfer was also achieved by all routes with cells washed three times although it was more difficult. Any of the three antigens could be used with subsequent reaction to the specific antigen although bovine serum albumin required the use of 7 mg. for tests. In the case of cells washed once, antibody and nitrogen estimations done on the wash indicated that amounts of antibody reported necessary for passive sensitization by circulating antibody were not present.

Reactions of recipients presented neither the appearance nor time sequence of typical Arthus reactions. Reactions began to appear five to eight hours after testing and reached a maximum at eighteen to twenty-four hours. The reactions persisted two or three days even with a minimal response and often as long as a week. Hemorrhage and necrosis were never observed, but edema and induration were prominent features.

Antibody could not be demonstrated in extracts of cells disrupted by grinding with powdered Pyrex, alternate freezing and thawing, or sonic vibration. Also, antibody could not be demonstrated in recipients' sera taken before testing, either by precipitin tests or sensitization of guinea pigs for anaphylactic shock.

Cells collected from normal donors did not transfer reactivity to the antigens. In addition, recipients exhibiting positive reactions to the specific antigen did not react to egg albumin or to normal rabbit serum.

Two experiments were done using the cornea of the recipient eye as testing site. In both cases positive reactions were seen with edema of the cornea. One reaction was minimal, disappearing by seventy-two hours. The other was intense, with ciliary injection and iritis as well as pronounced edema of the cornea. The latter reaction was maximal by forty-eight hours and healed gradually in about three weeks leaving a residual scar in the cornea. Normal animals gave no reaction to the procedure and donors showed an immediate conjunctival reaction which was absent in the recipients. More of these corneal tests are required to thoroughly establish this point.

By using cells pooled from several donors, dividing them equally among recipients, and then testing at time intervals after transfer varying from one-half hour to five days, it appeared that sensitivity of recipients could be demonstrated soon after transfer but increased to a maximum somewhere between two and five days. Of twenty recipients followed with daily tests, ten became negative before active sensitization ensued.

Although this investigation is far from complete, the time relationships of the reaction, absence of detectable circulating antibody and positive corneal tests all suggest that there is a delayed type sensitivity component in active sensitization by serum antigens.

* This work was done with Dr. Wayburn S. Jeter at the State University of Iowa College of Medicine, Iowa City, Iowa.

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Albert Lansing, Emory University School of Medicine, Atlanta, Ga.

PSYCHOLOGIC ASPECTS OF AGING
Ross A. McFarland, Harvard University

EXPERIMENTAL PROLONGATION OF THE LIFE SPAN
Clive M. McCay, Cornell University, Ithaca, N. Y.

Tuesday, October 11

ARTHRITIS IN THE ELDERLY PATIENT
Joseph J. Bunim, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland

THE EFFECT OF AGING ON THE MYOCARDIUM
William Dock, State University of New York College of Medicine at New York City, Brooklyn, N. Y.

FLUID AND ELECTROLYTE PROBLEMS IN SURGERY OF THE AGED
Henry T. Randall, Memorial Center for Cancer and Allied Diseases

RELATION OF INCREASED LONGEVITY TO NEOPLASIA
C. P. Rhoads, Memorial Center for Cancer and Allied Diseases

Wednesday, October 12

SOME PHYSIOLOGICAL ASPECTS OF AGING — *Wesley M. Carpenter Lecture*
N. W. Shock, National Heart Institute, Bethesda, Maryland

NUTRITIONAL PROBLEMS OF ADVANCING AGE
Fredrick J. Stare, Harvard University

GASTROINTESTINAL HEMORRHAGE IN ELDERLY PATIENTS
Thomas P. Almy, Cornell University Medical College

Thursday, October 13

PANEL MEETING — CEREBROVASCULAR DISEASE WITH AGING
Chairman: Irving S. Wright, Cornell University Medical College

Friday, October 14

PANEL MEETING — PROBLEMS OF RETIREMENT
Chairman: Howard Reid Craig, Director, The New York Academy of Medicine

(*Continued on next page*)

Second Week

Monday, October 17

THE NATURE OF THE RESPONSE TO STRESS WITH AGING — *Harlow Brooks Lecture*
James L. Whittenberger, Harvard University

EVALUATION AND PREPARATION OF THE PATIENT WITH DEGENERATIVE CARDIOVASCULAR DISEASE FOR MAJOR SURGERY
John S. La Due, The New York Hospital

THE AGING LUNG
Dickinson W. Richards, College of Physicians and Surgeons, Columbia University

Tuesday, October 18

MANAGEMENT OF INJURIES IN THE AGED
Robert H. Kennedy, Beekman-Downtown Hospital, New York

MANAGEMENT OF SURGICAL EMERGENCIES IN THE AGED
Condict W. Cutler, Jr., Goldwater Memorial Hospital, New York

SURGERY OF CHRONIC DISEASES IN THE AGED
Frank Glenn, The New York Hospital

ANESTHESIA IN THE AGED
Emanuel M. Papper, Presbyterian Hospital

Wednesday, October 19

EMOTIONAL AND PSYCHIATRIC PROBLEMS OF AGING
Francis J. Braceland, The Institute of Living, Hartford, Conn.

NEUROSURGICAL TREATMENT OF PARKINSONISM
Irving S. Cooper, New York University-Bellevue Medical Center

REHABILITATION IN THE AGED
Howard A. Rusk, New York University-Bellevue Medical Center

Thursday, October 20

PANEL MEETING — GONADAL FUNCTION AND INVOLUTION IN MAN — AND RELATED PRACTICAL MANAGEMENT
Chairman: Earl T. Engle, College of Physicians and Surgeons, Columbia University

Friday, October 21

PANEL MEETING — DISORDERS OF THE SPECIAL SENSE ORGANS ASSOCIATED WITH AGING: THEIR RECOGNITION AND TREATMENT
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Chairman: Henry S. Simms

Wednesday, October 12 — EVERYDAY PROBLEMS IN THE CARE OF THE AGED
Chairman: Frederic D. Zeman

Friday, October 14 — MANAGEMENT OF CARDIOVASCULAR RENAL PROBLEMS IN THE AGED
Chairman: Hugh Luckey

Second Week

Monday, October 17 — MANAGEMENT OF PROSTATIC OBSTRUCTION
Chairman: Robert S. Hotchkiss

Wednesday, October 19 — PUBLIC HEALTH ASPECTS OF AGING
Chairman: W. G. Smillie

Friday, October 21 — PROBLEMS OF INFECTIOUS DISEASES AND THEIR THERAPY IN THE AGED
Chairman: Perrin H. Long

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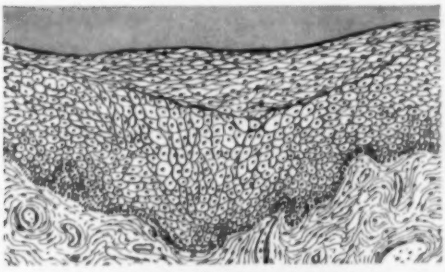
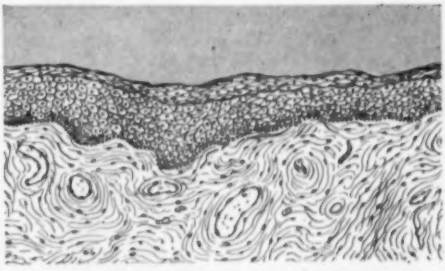
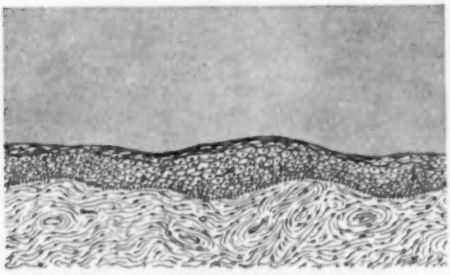


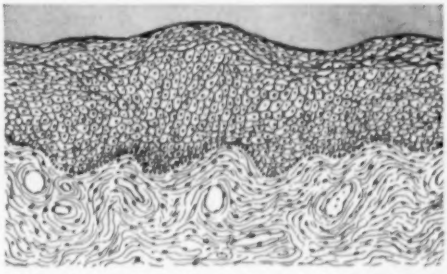
Adult vaginal epithelium maintained by estrogen activity.



During menopause, mucosa reverts to the infantile type.



Postmenopausal mucosa—thinning and atrophy of layers.



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*Sturnick, M. I., and Gargill, S. L.: New England J. Med. 247:829 (Nov. 27) 1952.

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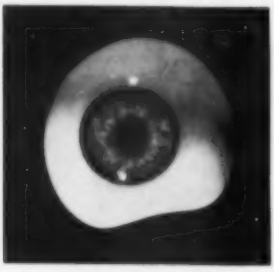

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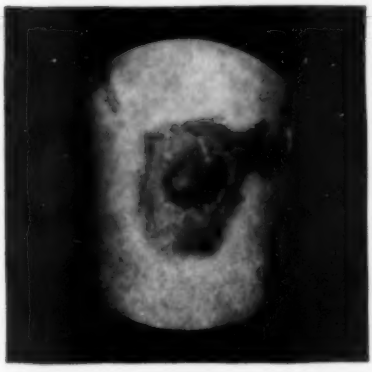

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Innerfield, I., *Trypsin Given Intramuscularly in Chronic, Recurrent Thrombophlebitis, J.A.M.A.*, 156:1056-1058 (Nov. 13) 1954. Golden, H., *Intramuscular Trypsin, Its Effect in 83 Patients with Acute Inflammatory Disorders, Del. State Med. J.*, 26:267-270 (Oct.) 1954.

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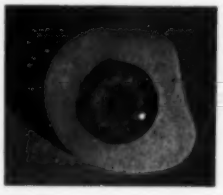

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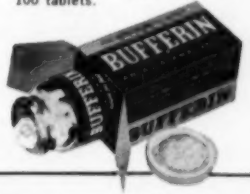

References: 1. Fremont-Smith, P.: J.A.M.A. 158:386, 1955. 2. J.A.M.A. 141:124, 1949. 3. M. Times 81:41, 1953.

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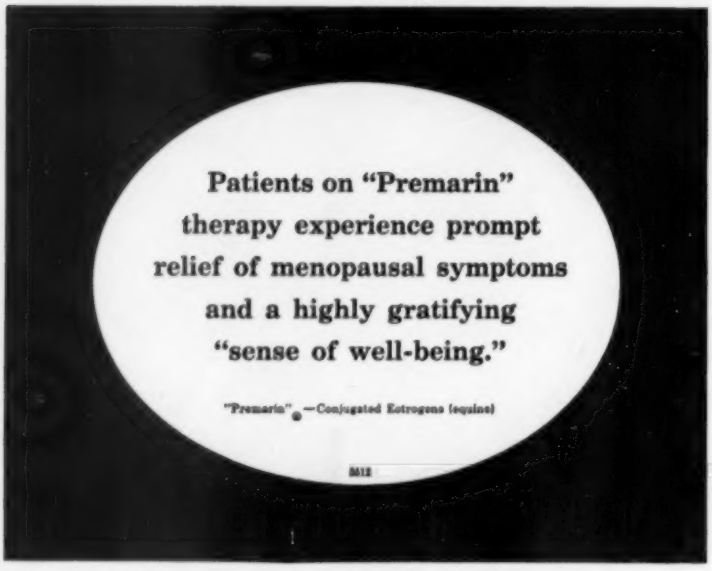

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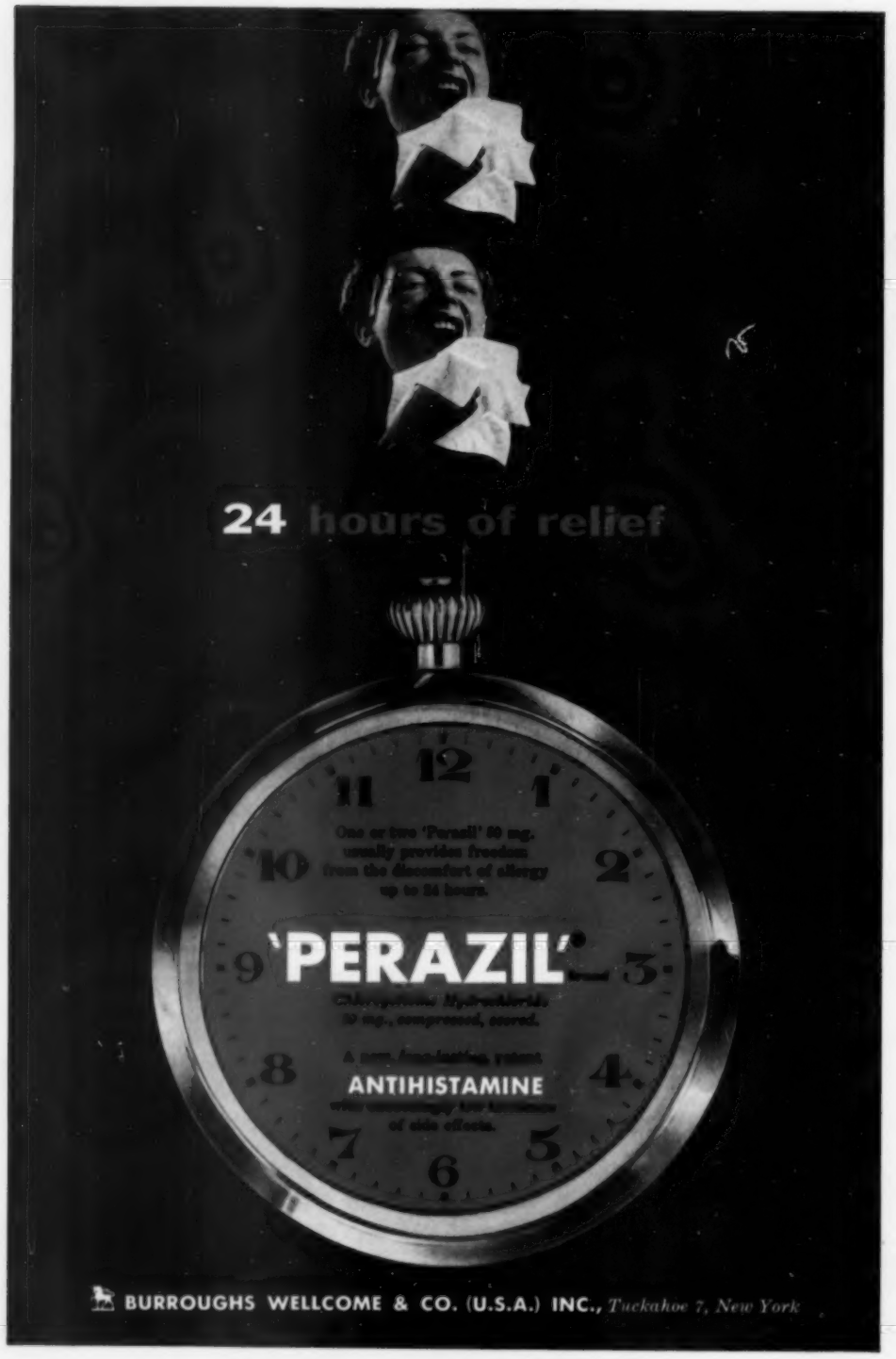
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